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OCTOBER, 1943

ORIGINAL ARTICLES

INTRADERMAL TEST FOR SUSCEPTIBILITY TO AND IMMUNIZATION AGAINST WHOOPING COUGH USING AGGLUTINOGEN FROM PHASE I H. PERTUSSIS*

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At the present time, 4 substances are available for use as reagents in skin testing for susceptibility to whooping cough. These are suspensions of killed *Hemophilus pertussis*, extracts of these bacterial cells, purified toxin and purified agglutinogen. The first 2 reagents have proven unsatisfactory because they represent gross mixtures of the several components of the bacteria and these individual components have conflicting reactive properties. Attempts to classify tested individuals into immune and susceptible groups with these 2 reagents have given confusing and overlapping results. Strean's results[9] with purified toxin indicate that this reagent does not distinguish between susceptible individuals and those who have been successfully immunized with killed whole Phase I *H. pertussis* cells, such as composed the vaccines of Sauer,[7] Kendrick and Eldering,[4] Miller and Faber,[5] Singer-Brooks,[8] and others. This purified toxin apparently distinguishes from the susceptibles only those recovered from the disease and those immunized with toxoid.

The rationale of the use of agglutinogen in such a test has been discussed previously.[2,3] Results obtained until now with the

* This is paper XI in a series "Studies with H. pertussis."

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test have shown that purified agglutinogen accurately classifies the immune and the susceptible individuals in accord with their histories, both of incidence of disease and of vaccination. A detailed analysis of some of the first clinical results obtained is reported elsewhere.[1] The test itself and the method of carrying it out are described here for the first time and the significance of the results is discussed. The total number tested and which are now being reported has been extended to 931.

Method. Ten units of agglutinogen in a volume of 0.1 ml. of 0.85% sodium chloride solution are used for intradermal injection. The container with dry agglutinogen is scratched with a file and opened in the usual fashion. The proper quantity of sodium chloride solution is added. The agglutinogen will be found to dissolve instantly, and after slight agitation it is withdrawn into a syringe. A preservative is not added because one not causing deterioration of the product or a false positive reaction in certain individuals has not been found. Unused agglutinogen should not be stored after dissolving, unless kept frozen, because of possible contamination.

The intradermal injection is made in the usual fashion. In immune children, two types of response may be obtained: the immediate or wheal-like reaction, and the delayed or tuberculin type of reaction. Some children may show both, some one or the other. Readings are made at two times, ½ hour and about 24 hours after injection. Induration is the determinant factor in a positive immune reaction to distinguish it from a negative susceptible reaction. Rubbing the finger over the site of injection frequently may aid in determining the extent of the reaction. Erythema may or may not be present and if present alone should not be considered. Erythema without at least some induration normally is not observed, and in the event that a non-indurated reaction should be suspected, it should be examined very carefully. If it definitely is nothing more than a flare of redness, the reaction should be classified as negative susceptible.

An area of 10 mm. is regarded as the upper limit for a negative reaction, this allowance being necessary because certain normal skins give a slight response to the trauma of the injection. No untoward local or systemic reactions have been observed in the approximately 1000 children tested so far.

The following has been used as a classification for grading the reactions:

PI—positive immune: a well-indurated reaction (with or without erythema) 20 mm. or more in diameter at either ½ hour or 24 hours or both.

WPI—weakly positive immune: an indurated reaction (with or without erythema) not exceeding 20 mm. in diameter at either ½ hour or 24 hours, but at least 10 mm. in diameter at either time or both.

NS—negative susceptible: no indurated reaction at either ½ hour or 24 hours beyond an area 10 mm. in diameter.

The reaction will be found to fade quickly, and usually in 36 hours or sooner will have disappeared. In negro children, immune or susceptible, some residual pigmentation may be observed, which is not abnormal in this race after intradermal injection.

Results. The results obtained in 650 children with known histories are summarized in Table 1. The histories were obtained from various institutions and clinics. Perhaps of greatest significance is the fact that only one child with a negative history showed a false positive reaction. The pattern or distribution of results obtained in those with positive histories of either the disease or of having been vaccinated is reasonable; a solid or even partial immunity in all individuals in these two positive groups is not to be expected. Among other factors

the children in the study having a positive history of the disease, did not have the diagnosis confirmed bacteriologically. There is always the possibility of *B. parapertussis* having been the causative agent and a positive immune reaction in such a case would not be expected. Some of those in the vaccinated group were from an institution where it was found subsequently that the vaccine used was of low potency.

TABLE 1.—RESULTS OF SKIN TESTING WITH AGGLUTINOGEN

	No history of disease or vaccination		History of whooping cough		Vaccinated	
Reaction	No.	%	No.	%	No.	%
Positive	1	<1	116	53	174	56
Weakly positive	0	0	78	36	114	36
Negative	121	>99	24	11	23	8
Total	122	100	218	100	311	100

The inclusion of an intermediate group, WPI (weakly positive immune) we believe should be of considerable interest. All immunity is relative. There are those with an intermediate or partial degree of immunity in whom the protection may be sufficient only when the exposure is not overwhelming and when the general resistance has not been lowered. The WPI group may serve to detect those individuals who have such a partial immunity.

In a child without known history of the disease or of vaccination, there may be some immunity as a result of contact or subclinical infection. It should not be surprising occasionally to find some degree of immunity indicated by the test in such a case. For this reason, in the present study, in the control group were included only babies within the age group of 6 to 14 months. In this group it is improbable that immunity might exist because whooping cough seldom occurs with sufficient mildness at this age to go undiagnosed. Under 6 months of age, of course, the skin cannot be assumed to act reliably.

A group of 281 "unknown" older children were tested. Of these, 45% showed a positive immune reaction, and 31% a weakly positive immune reaction.

Agglutination titers were determined in 173 children before skin testing. It was found that all those having an agglutination titer of 1 to 20 or higher give a positive, or weakly positive, skin test indicating at least some degree of immunity. On the other hand, individuals having no agglutination titer may also give a positive or weakly positive skin test indicating some degree of immunity. The explanation seems to be that the test is an indicator of fixed antibodies. On this basis the test is positive, at least to a limited extent, in all of those having circulating antibodies and also in those having only fixed antibodies and without detectable circulating antibodies. This suggests an explanation of the failure of agglutination titers to provide an accurate prediction of susceptibility to whooping cough, fixed antibodies not being detectable by agglutination. In harmony with these considerations Miller and collaborators, in a recent study with 554 children, have shown that whereas a negative agglutinative titer does not neces-

sarily indicate susceptibility, a significant positive titer does indicate clinical immunity.

It is striking that a single skin test injection of agglutinogen produces a marked rise in the agglutination titer of serum from those individuals showing a positive or weakly positive reaction initially. This increase in agglutination titer occurs regularly in all cases even though the titer initially may have been zero. (Of course, there is no increase in agglutination titer as a result of the test where initially the titer is high and close to the usual ceiling.) In some cases, the agglutination titer as a result of a single injection may rise from zero to as high as 1 to 10,000.

In 65 of the children, it was possible to obtain blood 10 months after the test had been performed. The agglutination titers were determined and it was found that in all cases the elevation in titer had persisted. In just a few cases, there was a slight decrease from the peak reached. None showed a major decrease in titer.

Those individuals giving a negative skin reaction require repeated skin test doses in order to reverse the test and to produce a significant agglutination titer. Usually 3 such doses are required.

These results suggest that agglutinogen might prove to be a valuable reagent for use in immunization, as well as for determination of susceptibility. Particularly would the reagent be of value for skin testing at some time following the primary vaccination. Used at this time in a single dose, the reagent would serve both to determine the degree of immunization resulting from the primary vaccination and as a "stimulation" reagent for immunization. This would fit in well with the currently favored procedure of stimulation of immunity to whooping cough at about a year following the primary vaccination in order to produce a more nearly complete immunity.

In a careful study of a small institutional epidemic, it was indicated that the use of agglutinogen as a skin test reagent accurately predicted susceptibility. Also apparently the partial immunity of many individuals was stepped up enough to protect them from the current infection. Thus the number of susceptible individuals was definitely decreased. From the epidemiologic point of view, this is a very fortunate finding because by means of this test not only are those few highly susceptible individuals singled out, but those with a partial immunity become more adequately protected.

Conclusion. It appears from this study that the purified agglutinogen of *H. pertussis* should provide, as expected,[2] an excellent reagent for assisting in control of whooping cough. This would be not only in detecting which individuals in a group are susceptible, but also in stimulating immunity in those having but a partial degree at the time of the test.

Summary. The skin test utilizing purified pertussis agglutinogen as reagent classifies immune and susceptible individuals in accord with their history of incidence of infection and vaccination with *H. pertussis*. The test can also be used as a means of stimulation of immunity sometime following primary vaccination, as well as to determine the degree

of immunity resulting from the primary vaccination itself. In those individuals having an existing immunity to pertussis at the time of the test, a marked increase is produced in the agglutination titer. In those with no initial immunity, repeated doses will produce a reversal of the test and an agglutination titer. The reagent gives promise of value, at the time of epidemics, not only to determine those who are susceptible, but also to increase the degree of immunity in those having but a partial immunity to pertussis.

ADDENDUM.—The preparation of agglutinogen following acid extraction has been described by Smolens and Mudd[8a]; this may be simpler as well as providing a method which can be more generally applied.

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THYROTOXICOSIS AS THE SOLE CAUSE OF HEART FAILURE

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ONE of the most brilliant advances in the modern treatment of heart disease concerns the small but significant group of thyrocardiacs. As a result of increased diagnostic facilities, the great improvement in preoperative medical care, and the advances in surgical technique, many patients suffering from even advanced congestive heart failure or incapacitating angina pectoris are restored to good health when they are found to have thyrotoxicosis. The general dictum that under proper care no thyrocardiac is too sick to be operated upon is almost literally true. It must be appreciated that these cases are peculiar, in that the ordinary measures employed in the treatment of heart failure prove ineffective and improvement and recovery only take place when the underlying burden of thyrotoxicosis is removed. In that sense they constitute possibly the largest group of so-called curable or reversible heart disease. Numerous publications have appeared during the past two decades emphasizing the importance of recognizing the less obvious of these cases which have been called

"masked thyrocardiacs." Despite this great interest, fairly competent physicians still overlook these cases for many months or years, permitting invalidism to continue that is entirely unnecessary.

One of the practical difficulties in this problem is that when the obvious evidence of hyperthyroidism (exophthalmos and thyroid enlargement) is absent these patients have the symptoms and signs of heart failure similar to those that are commonly met with in general practice in patients who have no hyperthyroidism. In other words they are not unlike those who have hypertensive heart disease, coronary artery disease, rheumatic valvular disease, or any other common form of heart disease. The difficulty is increased because of the fact that most thyrocardiacs with heart failure also have these additional burdens on the circulation. The result is they are treated for valvular disease, coronary artery disease, or hypertensive heart failure (which they often have) and the additional thyrotoxicosis is entirely overlooked. Finally, thyrotoxicosis *per se* may produce signs and symptoms which closely simulate those found in mitral stenosis.[7] Under such circumstances, the physician may treat a case for mitral stenosis when no such lesion is present and when the entire illness is due to "masked hyperthyroidism." The methods employed in detecting "masked hyperthyroidism" have been adequately discussed in the past[8] and will not be taken up here.

It has long been known that when hyperthyroidism is associated with heart failure there is almost always some other independent type of heart disease. In fact, this has been so common and so striking that some authorities would lead us to believe that thyrotoxicosis alone never produces heart failure.[6] To be sure, one is frequently impressed by instances in which a thyrotoxic state has persisted for many years without any failure. However, there have been reported cases of heart failure in which no other etiologic factor could be detected except hyperthyroidism.[5] Some investigators are tempted to explain these latter cases on the basis that heart failure occurs because of unrecognized coronary artery disease, myocardial fibrosis, or other senile changes.[4] It is the purpose of this paper to offer clinical evidence indicating that thyrotoxicosis can be the sole cause of congestive heart failure.

All cases with thyrotoxicosis in which a subtotal thyroidectomy was performed at the Peter Bent Brigham Hospital between 1923 and 1941, inclusive, were analyzed in this study (Table 1). All those regarded as having increased thyroid function whether as a part of diffuse hyperplasia or toxic adenoma were included. There were 409 such cases, 314 females and 95 males, a proportion of more than 3 to 1. These were divided into two groups: "non-cardiacs" (331 or 81%), and "cardiacs" (78 or 19%). The former consisted of those instances in which no other type of heart disease, apart from thyrotoxicosis, existed. The latter 78 cases included 45 with hypertensive heart disease (the blood pressure being found above 150/90 on repeated examinations), 20 with definite rheumatic valvular disease, 12 with either angina pectoris or coronary thrombosis, and one with syphilitic

aortic insufficiency. Further analysis showed that 4 of the rheumatics and 8 of the coronary cases had hypertension in addition, indicating that there really were 57 cases with hypertension. It also may be added that 2 with rheumatic heart disease had definite angina, increasing the total of the coronary group to 14. It is obvious that independent organic heart disease is not uncommon in patients with thyrotoxicosis. The large number (5% of the entire 409) with rheumatic valvular disease is particularly impressive, for the expected incidence of rheumatic heart disease in the population of this community is no more than 1% to 2%.

TABLE 1.—THYROTOXICOSIS WITH SUBTOTAL THYROIDECTOMY
(PETER BENT BRIGHAM HOSPITAL, 1923–41)

	No. of patients	Females	Males	Average age (yr.)	Average duration of thyrotoxicosis (mo.)	Auricular fibrillation
"Non-cardiacs":						
Compensated	310	240	70	40	8	22
Decompensated	21	19	2	44	29	8
Severe	8	7	1	45	55	7
Moderate	13	12	1	43	12	1
Total	331	259	72	40	9	30
"Cardiacs":						
Compensated	39	28	11	53	7	6
Decompensated	39	32	7	52	10	23
Severe	23	19	4	52	9	20
Moderate	16	13	3	52	11	3
Total	78	60	18	53	8	29
Hypertensives:						
Compensated	27	19	8	54	8	5
Decompensated	18	15	3	57	11	8
Total	45	34	11	55	9	13
Coronary artery disease:						
Compensated	8	5	3	56	7	1
Decompensated	4	4	0	61	10	3
Total	12	9	3	58	8	4
Rheumatic heart disease:						
Compensated	4	4	0	43	6	0
Decompensated	16	13	3	44	8	12
Total	20	17	3	44	8	12
Luetic heart disease	1	0	1	52	8	0
Grand total	409	319	90	42	9	59

Of greater interest was the occurrence of congestive heart failure. By this term is meant the appearance of objective evidence of congestion, such as pulmonary râles, hydrothorax, enlarged liver, and peripheral edema in addition to the subjective complaints of dyspnea, cough, palpitation, and weakness. Patients having only subjective symptoms such as palpitation (even if auricular fibrillation were present), or breathlessness, and those showing definite cardiac enlargement, but without the objective signs enumerated above, were not regarded as having heart failure for purposes of this study. The history of swelling of the feet was very common in this group, but was not sufficient to classify the case as having heart failure unless pitting edema was observed in the hospital. The degree of heart failure was

further divided into two groups, severe and moderate. The former had definite hydrothorax or large palpable liver (generally both), with or without ascites, while the latter had significant pitting edema, râles at bases of lungs, in addition to the symptoms of myocardial insufficiency.

Among the 78 cases of thyrotoxicosis having some additional form of organic heart disease, there were 23 with severe and 16 with moderate congestive heart failure (50%). What is more significant is that in the "non-cardiac" group (331 cases) there were 8 with severe and 13 with moderate failure (6.3%). These latter 21 cases supply the main evidence that thyrotoxicosis alone may cause heart failure even when the blood pressure, the coronary arteries, and the valves are normal. The following case history is a striking example.

H.W. (M. 58597) female, age 34, entered P.B.B.H. December 19, 1940. There was no past history of rheumatic fever or chorea. She was apparently well, though slightly tired, until December, 1939. She then had "intestinal flu," with some nausea and diarrhea, and was in bed about 6 weeks. After this she first noticed shortness of breath, but was able to carry on. In June, 1940, she first noted a rapid, irregular beating of the heart, a generalized erythematous rash, and marked increase in breathlessness. She had been in bed off and on ever since. On several occasions fluid was removed from her right chest by tapping. The appetite had been good most of the time. During recent weeks there was some swelling of abdomen, ankles, right arm, and right side of face (patient had been lying on right side most of the time).

Physical Examination. Patient seemed to be acutely sick. There were numerous punched-out, crusting, erythematous pustules all over her body. Almost the entire right chest was flat with diminished breath sounds. The apex impulse was felt at the left anterior axillary line. The rhythm was grossly irregular, and the sounds hyperactive. There was a Grade II apical systolic murmur, but no diastolic murmur could be heard. The blood pressure was 130/60. The cervical veins were moderately distended. The liver extended a hand's breadth below the costal margin and there was moderate ascites. There was some pitting of the sacrum but not of the legs.

The first impression here was that we were dealing with a case of mitral stenosis and auricular fibrillation. This diagnosis was supported by the finding of marked right axis deviation in the electrocardiograms and a dilatation of the left auricle on fluoroscopic examination. Further studies, however, seemed to point more and more to diagnosis of hyperthyroidism. The velocity of blood flow was found to be 14 seconds. The B.M.R. ranged between +33 and +47. Venous pressure was 175 mm. Vital capacity was 500 to 800 cc. The urine and blood were not abnormal. Although there was considerable doubt as to the diagnosis in the minds of many physicians who saw her, as there was no exophthalmos or definite thyroid enlargement, she was given Lugol's solution and otherwise continued on the same cardiac management as before, *i. e.*, digitalis, mercupurin, and chest taps. She gradually improved, although she still had a considerable hydrothorax. The B.M.R. fell to +12. A one-stage subtotal thyroidectomy was performed January 13, 1941. Pathologic examination of the gland showed diffuse hyperplasia with iodine involution. She continued to improve in an amazing fashion. Because the auricular fibrillation persisted she was given quinidine on January 23, and after a few doses of 0.3 gm., the rhythm became regular. Right axis deviation persisted in the electrocardiograms. The postoperative B.M.R. was +2%. Recovery thereafter was complete so that now, 2 years after operation, the patient is perfectly well doing full duties as a housewife, and has no signs or symptoms of heart disease.

Analysis of the *sex* relationship among these patients reveals the fact that women bear thyrotoxicosis less well than men. It was found that while the proportion of female to male among those who did not have heart failure in the "non-cardiac" group (310 cases) was $3\frac{1}{2}$ to 1, the proportion for those who went into failure was 10 to 1 in favor of females. The corresponding figures for the 78 cases belonging to the "cardiac" group were $2\frac{1}{2}$ to 1 for those without heart failure and $4\frac{1}{2}$ to 1 for those with failure. It is not clear from this study why women are more likely to have heart failure as a result of hyperthyroidism.

It is to be expected that *age* would play a rôle in determining the development of congestive failure. Older patients might have undetected degenerative changes in the myocardium more frequently and are also more likely to have had the thyrotoxic state for a longer time. This is borne out by the fact that patients with coronary artery disease and congestive failure were on the average 5 years older (61 years) than those without failure (56 years). Likewise, the hypertensives were 3 years older on the average (57 years) when congestive failure was present than when absent (54 years). Even the thyrotoxic patients without other etiologic types of heart disease were 4 years older (44 years) when congestive failure was present than when absent (40 years). It must not be inferred, however, that heart failure from thyrotoxicosis can occur only in the aged. In this study there were 6 instances of congestive heart failure in patients under the age of 40, and 3 under the age of 30 when there was absolutely no evidence of other lesions such as rheumatic valvular disease, hypertension, or coronary artery disease.

Another possible factor in the production of heart failure might well be the *duration* of thyrotoxicosis. It would seem that the longer the deleterious effect of hyperthyroidism might continue the more likely the heart would fail. It was not a simple matter to analyze this point, as often the onset of thyrotoxicosis could be determined only with difficulty. It is of interest, however, that the duration of thyrotoxicosis in the "non-cardiac" group with severe failure was 55 months, with moderate failure 12 months, and with no failure 8 months. It was to be expected that heart failure would result sooner in those already having organic heart disease. This proved to be the case, for the duration of thyrotoxicosis in the "cardiac" group with failure was only 10 months. The important inference is that if thyrotoxicosis remains uncontrolled for years it may eventually produce heart failure even if there is no preëxisting heart disease.

It has long been known that *auricular fibrillation*, either paroxysmal or permanent, is frequently a part of the clinical picture of thyrotoxicosis. The paroxysmal form is common, particularly directly after the operation, in cases showing very little evidence of cardiac involvement and no evidence whatever of heart failure. Permanent fibrillation, however, is much more likely to be associated with other types of heart disease or severe heart failure. In this present analysis only cases known to have permanent fibrillation were considered. It is of interest that among 78 cases belonging to the "cardiac" group there

were 23 with severe heart failure of which 20 were fibrillating, and 16 with moderate failure of which 3 were fibrillating. Among the 20 with rheumatic heart disease, 16 were in failure of which 12 had auricular fibrillation, and the 4 who were compensated all had a normal rhythm. Among the 57 cases with hypertension or coronary artery disease, 22 were in failure of which 11 had auricular fibrillation, and 35 were compensated, 6 having auricular fibrillation. In contrast to the "cardiac" group, there were 331 "non-cardiac" cases of which 21 were decompensated. Eight were in severe failure, 7 of which were fibrillating, and 13 were in moderate failure, only 1 of which was fibrillating. Of the 310 who were compensated, 22 were fibrillating. It follows that if congestive failure is present, fibrillation will be very frequent in the rheumatic group, less common in the hypertensive and coronary group, and least frequent in the "non-cardiac" group. Furthermore, when fibrillation does occur in a rheumatic case one may expect that failure will always be present; when this arrhythmia accompanies hypertension or coronary artery disease, decompensation will be expected in 65% of the instances, and when it is found in a "non-cardiac" case of hyperthyroidism the incidence of failure is 27%. The close relationship between auricular fibrillation and heart failure is also apparent in the following figures. The incidence of auricular fibrillation in the "non-cardiac" group without failure was 7%, while with failure it was 38%. The incidence in the "cardiac" group without failure was 15%, and with failure 59%. The irregularity, therefore, was 4 or 5 times as frequent when heart failure was present than when it was not. It was even more frequent in the presence of heart failure in those having no organic heart disease than in those having independent heart disease but no congestive failure.

The similarity between mitral stenosis and thyrotoxicosis has already been mentioned. Both conditions obviously are accompanied by symptoms of cardiac disability, such as dyspnea, palpitation, weakness, and congestive failure, and both conditions may present similar findings on physical examination, *i. e.*, cardiac enlargement, transient or permanent fibrillation, accentuation of first heart sound, systolic murmurs, and slight apical thrill. To be sure, the thrill in mitral stenosis is presystolic and in hyperthyroidism is systolic, but when the heart rate is rapid it is often impossible to make this distinction on palpation. The one distinguishing point is the diastolic murmur which does not occur with thyrotoxicosis. On the other hand, this tell-tale sign may be absent in mitral stenosis in some cases, or inaudible when the rate is rapid. The great frequency of the coëxistence of mitral stenosis and thyrotoxicosis may further complicate the diagnostic problem.

The additional point we wish to make at this time is that the Roentgen ray evidence of mitral stenosis may also add to the confusion. It is well-known that enlargement of the left auricle especially posteriorly is a very early and valuable sign of mitral stenosis. Some enlargement of the left auricle was observed in 8 of 17 cases in this series that had heart failure from thyrotoxicosis *per se*. Although this left auricular enlargement was not very marked, it was no less in degree than many

cases of early mitral stenosis show and sufficient to suggest mitral disease from a roentgenologic point of view. Enlargement of the pulmonary artery has been noted by Parkinson and Cookson,[11] but no mention was made of a similar enlargement of the left auricle. The fact that this left auricular dilatation is a part of the thyrotoxicosis is confirmed by the observations made in these instances after the metabolism had returned to normal and cardiac compensation reëstablished. Five cases that had shown dilatation of the left auricle on fluoroscopic examination preoperatively failed to show this change postoperatively. It might be thought that the fibrillating state of the auricles rather than the hyperthyroidism caused the slight dilatation of the left auricle. That this is not the case is borne out by the fact that left auricular dilatation was found in some cases with a regular rhythm and was observed to decrease in extent after operation when the metabolism was normal even while fibrillation continued. It follows, therefore, that dilatation of the left auricle in some cases is a specific result of thyrotoxicosis.

Discussion. It is abundantly clear from an analysis of the cases in this study that congestive heart failure of a mild or even of extreme degree can result from thyrotoxicosis when careful search fails to reveal any of the other common etiologic causes of heart disease such as valvular disease, hypertension, or coronary sclerosis. Although this has been noted by other observers, its importance and frequency has not been sufficiently emphasized. In fact, the frequent finding of these other forms of heart disease in patients with hyperthyroidism who have congestive failure has led to the view that hyperthyroidism alone does not produce heart failure. This prevailing opinion is particularly unfortunate because it tends to make physicians overlook this small but important group of thyrocardiacs in which heart disease is actually curable or reversible. When the obvious evidence of thyrotoxicosis such as exophthalmos and thyroid enlargement is not present, one is too ready to regard these patients as having incurable heart failure from mitral stenosis, myocardial degeneration, hypertension, or coronary artery disease when none of these complications is present. One might add that even if they were present, it still is extremely important to discover the added burden of thyrotoxicosis, for the latter can be removed whereas the former cannot.

If one still had doubt concerning the absence of other forms of heart disease in the group of 21 cases that had congestive failure from thyrotoxicosis alone, it can be dispelled by the evidence furnished from the follow-up study. After an average period of 5 years (the longest was 10 years), none of these patients showed any evidence of organic heart disease. There were 4 deaths during this period, all from carcinoma. All the others were essentially well.

It is difficult to explain the mechanism of heart failure when it is the sole result of thyrotoxicosis. It is obvious that hyperthyroidism can continue for years in some cases without producing heart failure. Is it purely the result of increased work? Obviously there is increased work of the heart that continues even with the patient at rest when the

basal metabolic rate is abnormally elevated. It is difficult to believe that this is the only factor involved. Is there a specific or non-specific toxic factor that injures the myocardium? There are rare reported examples of focal myocardial necrosis associated with hyperthyroidism.[2] The auricular fibrillation so common in hyperthyroidism may well be looked upon as a toxic manifestation, for the arrhythmia may even precede the elevation in the basal metabolism. Once auricular fibrillation has developed, it can be an added factor in the causation of heart failure, for prolonged uncontrolled auricular fibrillation in an otherwise normal heart may result in heart failure.[1,9] Finally, one cannot escape the similarity between some of the clinical features seen in heart failure from beriberi disease and thyrotoxicosis. Several years ago Soma Weiss suggested that some of the features of thyrotoxicosis could well be due to vitamin B deficiency.[13] A similar view has been held by Means.[10] This possibility was not investigated in this study although during the past few years, since the importance of vitamins has been more fully appreciated clinical evidence of deficiency states, such as red palms and sore, smooth, red tongue has been repeatedly observed in these thyrocardiacs. This whole subject is quite important and deserves further study. It probably will be found that cases of hyperthyroidism with heart failure will show much more chemical and clinical evidence of vitamin deficiency (especially the B complex) than those without heart failure. If this concept is correct it ought to be true that with the same metabolic rate, thyrotoxic patients with heart failure will be found to have had a poorer appetite, and to have taken a poorer diet, than those without heart failure.

There is another practical consideration with regard to the surgical treatment of these patients that seems important. At first glance one might feel that these severe thyrocardiacs, having not only thyrotoxicosis but advanced heart failure, would prove to be the most difficult and the most serious from a surgical point of view. In fact, this view is so current that many physicians and surgeons advise multiple stage operations for such severe cases.[6] We have had quite the contrary view in this clinic. It has been our impression that the operative mortality and incidence of alarming thyroid storms have been no more or even less in the older, severe thyrocardiacs than in the younger cases of exophthalmic goiter. This was borne out by the following analysis: There were no instances of thyroid crisis among the 60 patients who had heart failure, while of the remaining 349 that had no heart failure, 18 developed a thyroid storm. Even more important were the differences in the operative mortality. There were 8 deaths in 310 cases showing no evidence of heart disease or heart failure (2.6%). In contrast there were no fatalities among 21 "noncardiacs" with heart failure, and 78 cardiacs, half of whom had heart failure.* It is difficult to explain the discrepancy between the absence

* One of these latter cases was literally moribund and unconscious at the time of operation, which was performed as an emergency procedure for an intrathoracic goiter. The surgeon feared the patient would not leave the operating room alive if not operated upon. He died 1 hour postoperatively.

of any operative mortality in this latter group and the occurrence of 4% mortality among thyrocardiacs in the Lahey Clinic as reported by Hurxthal.[4] The outstanding impression we have had is that the severe thyrocardiac never worries us before, during or after the operation. It is the younger individual with classical Graves' disease that may suddenly develop a severe or even fatal crisis. Furthermore, it is not without significance that all but 7 cases had one-stage operations. This is also in conflict with the prevailing teaching.[4,12] If multiple stage operations are necessary in thyroid surgery, they do not appear to be indicated in the group of cases under consideration that show heart disease or heart failure.

Summary and Conclusions. 1. A study was made of 409 cases of thyrotoxicosis operated upon at the Peter Bent Brigham Hospital from 1923 to 1941, inclusive. There were 331 (81%) "non-cardiacs" and 78 (19%) "cardiacs." Among the latter there were 45 with hypertensive disease, 20 with rheumatic heart disease, 12 with coronary artery disease, and one with syphilitic aortic insufficiency.

2. There were 39 cases of heart failure among the 78 "cardiacs" (50%), and 21 instances of definite congestive failure among the 331 "non-cardiacs" (6.3%). It is apparent, therefore, that thyrotoxicosis not infrequently is the sole cause of congestive heart failure.

3. It was found that congestive failure was more likely to occur in the female sex, with increasing age, when the thyrotoxic state lasted longer, and when auricular fibrillation was present. No satisfactory explanation was found for the heart failure especially in the "non-cardiac" group. It is suggested that vitamin B deficiency may play a contributory part.

4. The similarity between symptoms and physical findings in mitral stenosis and thyrotoxicosis may lead to errors in diagnosis, for even left auricular dilatation on Roentgen ray examination is found in the latter condition.

5. In 99 cases with cardiac involvement there was no surgical mortality. All but 7 of these had a one-stage subtotal thyroidectomy. The surgical mortality in 310 cases without heart disease, however, was 2.6%. We, therefore, do not believe that the so-called severe thyrocardiacs require a multiple stage operation, and feel that they cause less concern than the younger exophthalmic goiter when surgical treatment is planned.

6. It is evident that "masked thyrotoxicosis" is being overlooked as a cause of heart failure, an error which is very costly because the condition is curable.

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THE CONTROL OF POLYCYTHEMIA VERA BY VENESECTION

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Patients with polycythemia vera usually obtain symptomatic relief from measures which reduce the excess of circulating erythrocytes. The excess may be destroyed by phenylhydrazine, removed by venesection or reduced by the suppression of bone marrow activity from

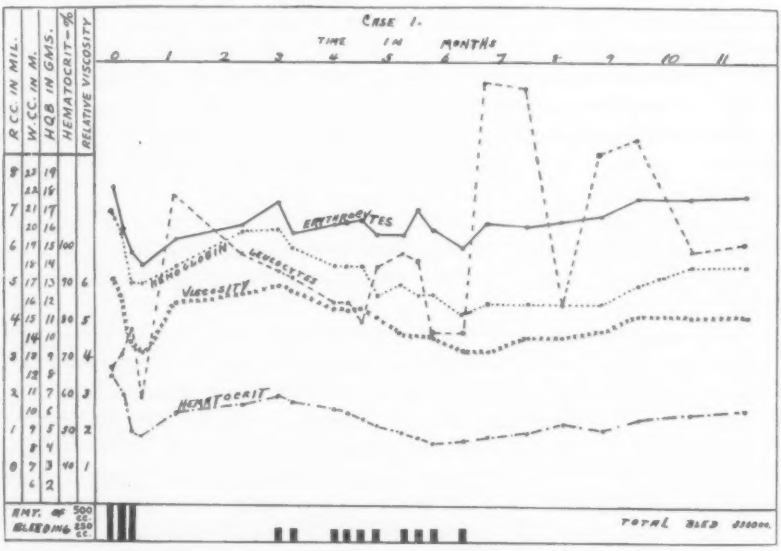

Fig. 1.—Changes in blood findings.

Roentgen irradiation or other injectable irradiated elements. The use of irradiation and phenylhydrazine has been criticized because the destructive power of the agent cannot always be completely controlled. In spite of this potential danger irradiation in one form or another is the most widely used method of treatment. The commonly accepted view that venesection is not wholly satisfactory for this disease is expressed by Harrop[1] as follows: "One must conclude that while

venesection is an important and useful relief in emergency in the treatment of these patients it cannot be looked upon in any other light

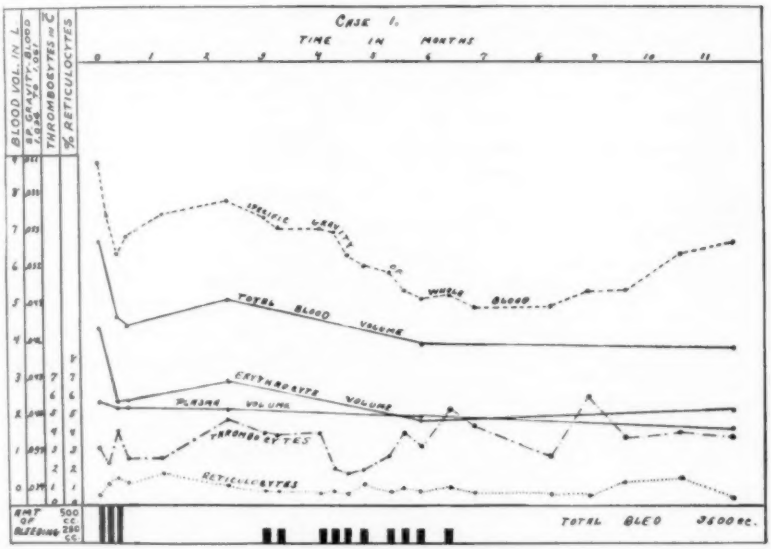

FIG. 2.—Changes in blood findings.

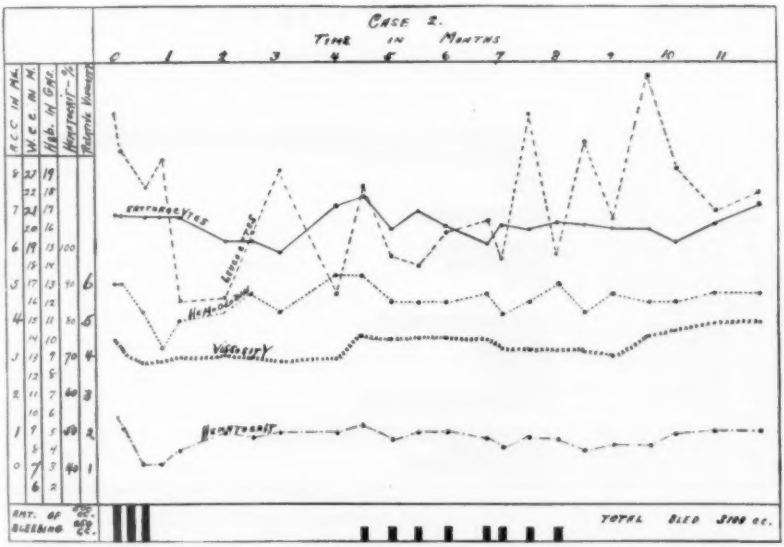

FIG. 3.—Changes in blood findings.

than as a further and therefore undesirable stimulant to new blood formation."

The difficulty in evaluating therapy of any disease is accentuated in

the case of polycythemia vera because spontaneous changes occur normally. Rosenthal and Bassen[2] have recorded a variety of stages and unusual manifestations such as symptomless periods, spontaneous development of anemia, periods with great leukoblastic activity or with thrombocythemia. Despite such obstacles for accurate inter-

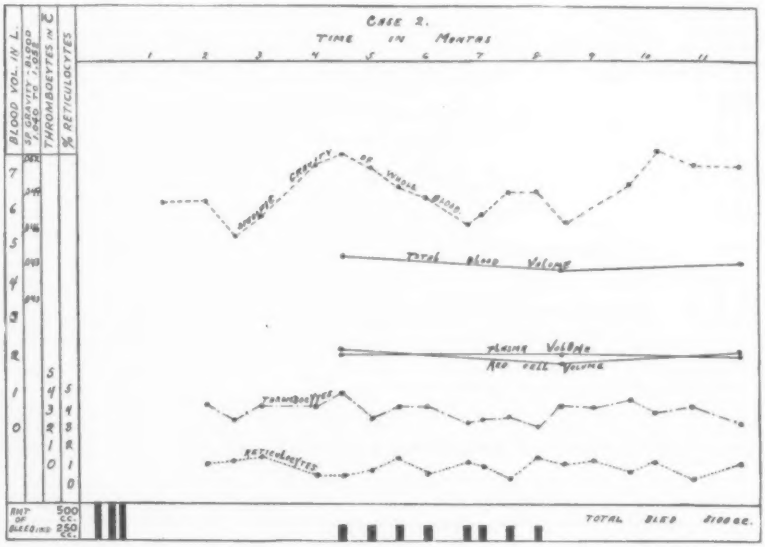

FIG. 4.—Changes in blood findings.

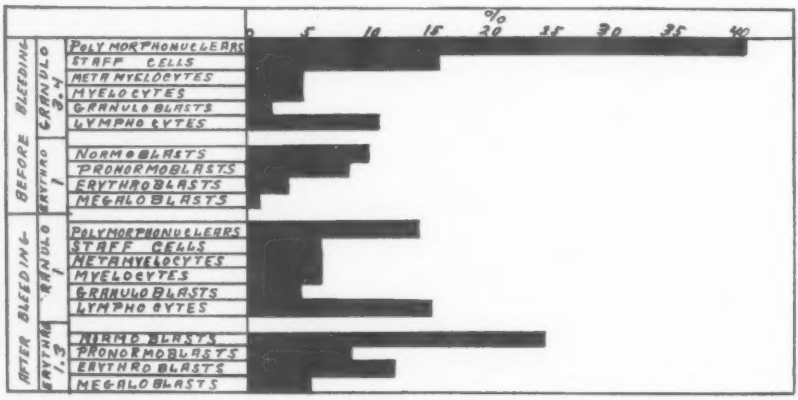

FIG. 5.—Differential bone marrow puncture—Case 1.

pretation a detailed study of two patients for more than a year suggests that venesection, properly used, is a safe method for adequately controlling the disease.

Hemoglobin was studied by the Sahli method; blood and plasma volume by the Evans blue method; blood and plasma viscosity with a

Hess viscosimeter and specific gravity of whole blood and plasma by the falling drop method. For hematocrit estimations heparin was the anticoagulant. In both cases the diagnosis of polycythemia vera was confirmed by computing the volume of circulating erythrocytes. By estimating the excess over normal it was possible to calculate the approximate amount of blood to be removed.

At first an attempt was made to eliminate the excess quickly by removing as much as 1500 cc. in a 14 day period. This produced a marked fall in erythrocyte volume, hemoglobin, specific gravity and viscosity. Partial symptomatic relief of certain symptoms (tingling of fingers, fullness in the head and generalized aching) was obtained, but undesirable symptoms were also produced. Evidence of erythropoietic stimulation (slight rise in reticulocytes and changes in bone marrow cytology) added to unwanted effects. Then we decided to study the effects of removing smaller amounts at intervals of about 2 weeks. By using a syringe of 100 cc. capacity that contained 5 cc. of sodium citrate solution, 200 to 250 cc. could be removed as simply as any other office procedure. At once we found that no symptoms were produced by small venesections. Figures 1 to 4 record the changes in blood findings over a 12 month period and allow a comparison of the effects produced by the two methods. When the small venesection was employed there was a gradual reduction of hematocrit values, blood viscosity, and hemoglobin. This effect was in sharp contrast to that produced by the large venesection in which a sharp fall was followed by an equally steep rise. After repeated small venesections it was observed that the fall in hemoglobin was not equaled by a corresponding fall in numbers of circulating red cells, because the latter had become microcytic. When the computed excess had been removed, bleedings were discontinued. For several weeks the patients remained asymptomatic with only slight developments toward an erythremic state. Four months after cessation of bleeding in Case 2, and 5 months after in Case 1, the return of symptoms was associated with rise in hemoglobin and erythrocyte volume. Again a series of small bleedings was instituted. In both cases spleen size was reduced by removal of blood and became larger when erythrocyte volume rose. In this disease it is obvious that an estimation of erythrocyte volume is the best guide for therapeutic need. Technical difficulties prevent widespread repeated use. It appears that a hematocrit reading alone with hemoglobin estimations and erythrocyte counts serves as an adequate substitute. Blood viscosity or specific gravity determinations offer no advantages, either of accuracy or simplicity.

Conclusions. The following method for the control of symptoms of polycythemia vera is suggested: To determine the actual excess of circulating erythrocytes as well as confirm the diagnosis, an estimation of the total erythrocyte volume is made; at weekly or bimonthly intervals 200 to 250 cc. of blood is removed by venesection; this may be carried out in the office by using 100 cc. syringes; the bleedings are continued until the computed excess of erythrocytes is removed or until hematocrit, hemoglobin and erythrocyte counts reveal beginning

anemia; bimonthly estimations of hemoglobin, erythrocyte counts and hematocrit will detect recurrence of the erythremic state and point out the need for further venesections. Two patients treated by this method for more than a year have remained free from symptoms.

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OBJECTIVE METHODS TO DETERMINE THE SPEED OF BLOOD FLOW AND THEIR RESULTS (FLUORESCEIN AND ACETYLENE)*

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The determination of velocity of blood flow has gained a definite place in the examination of cardiac patients and in those with endocrine disturbances or pulmonary disorders which impair the flow of blood through the lungs. If this diagnostic procedure has not yet found general adoption, it is mainly because the available methods were either subjective and thereby carried a certain intrinsic fraction of unreliability or, when objective, the complicated apparatus required considerable laboratory facilities. Furthermore, the subjective method fails precisely in those cases where the determination of the circulation time has decisive value, namely in unconscious patients and in children with congenital heart diseases. Moreover, the subjective factor implicit in many methods is responsible for some of the dubious results obtained and tends to discredit the basic valid conception itself. Finally, some methods in use were not free from danger. Fatalities and serious complications after the determination of circulation time have been reported and have further discredited these methods.[6,14]

The inhalation of carbon dioxide by the method of Bornstein[5] belongs, to some extent, among the objective procedures. However, the threshold of response in the centers involved may be quite different individually and, as Berliner[2] has shown, may vary even in the same person under different conditions. Furthermore, it necessitates considerable equipment and is scarcely applicable in children and in unconscious patients.

The lobeline method fails to evoke a response in all patients, and is subject to the same criticism. The same objection holds for the sodium cyanide method; in addition it may cause syncope and respiratory arrest.[17]

The use of radioactive substances[4] requires rather elaborate equipment and is not free of danger. The histamine method[19] is also not

* Aided by a grant from the John and Mary R. Markle Foundation.

devoid of danger, as the authors state themselves. It also is apt to fail in certain individuals, especially when lung pathology is present.

Koch[11] was the first to use fluorescein for the determination of the speed of blood flow. He injected it into the antecubital vein of one arm and withdrew blood from the other arm, taking a specimen every 5 seconds and watching for the first appearance of luminescence in full daylight. This method, although harmless, is rather inaccurate and somewhat complicated.

In 1931, Lange and Wollheim[20] demonstrated that an adequate source of light makes fluorescein emit a luminescence sufficiently strong to be seen in human vessels of small caliber. However, the available sources of light required for such an examination were somewhat clumsy and not readily applicable in general practice. Since that time we have simplified the method that it can now be considered practical for general use.

The appearance of the fluorescein can also be observed in all parts of the intestine when the peritoneal cavity is opened as well as in the skin of the entire body to give objective information about peripheral vascular diseases and inflammatory reactions.[10,12]

In a circulation-time test one determines the speed of blood flowing fastest in the axis of the vessel from the point of injection to the point of observation. Since the estimation is made in a single segment of the circulation the result does not necessarily obtain for the entire vascular system, because different conditions may prevail in another circuit. Accordingly, it must be proven under conditions in which the circulation in one single circuit is not especially rapid or slow that the determination of the circulation time, gives an exact picture of the average circulation time. To avoid the mistake of employing an abnormal circuit, 5 conditions must be fulfilled: (1) The circuit must contain all essential parts of the circulatory apparatus, that is, a vein, the pulmonary circulation, an artery, arteriole and capillary. (2) The circuit must be at basal conditions for the given individual; it must not have abnormally dilated arterioles or capillaries created by purely local factors. (3) The point of observation should permit the detection of the arrival of the test substance in the capillaries and not in the smaller arteries or arterioles. (4) The quantity of material injected must be sufficiently large to require several contractions of the heart for ejection in order to avoid any mistake created by the material passing the point of examination without detection on its first passage or being shunted into unobserved circuits by abnormal stream conditions. (5) The injected material should not influence the velocity of blood flow.

Very recently, Fishback[7] and his associates modified our original method; in place of using the lips as a point for observing the appearance of the fluorescein they chose the conjunctiva and the sclera. Under these circumstances, the conditions (2) and (3) mentioned above are not fulfilled. According to Mueller and Laube[13,15] the vessels of the conjunctiva are extremely sensitive to touch and dilate readily, and all types of vessels (small arteries, arterioles, capillaries and

venules) can be easily observed and hardly distinguished from each other without recourse to a capillary microscope. This may explain the wide variations of values obtained by these observers. Moreover the direction of the ultraviolet light to the eyes causes some discomfort and this factor alone may change the vascular status. The retraction of the eyelids required by this modification certainly changes the local vascular status.

Nature of Fluorescein. Fluorescein is resorcinophthalein. It is readily available, inexpensive and non-toxic. One gram has been given orally as a test of renal function without any deleterious effects;[18] as much as 6 gm. have been given by the same route to stain certain parts of the eye; no untoward symptoms follow although the skin may be stained yellow for 12 to 30 hours under these circumstances.[9] Fluorescein undergoes no change in the body and is rapidly excreted in the urine. In over 600 injections we have given so far we had 3 instances of slight nausea for about 1 minute. In these 3 cases, 10 cc. of the fluorescein solution were injected too rapidly intravenously since peripheral vascular studies were intended.

When examining the physical properties of fluorescein for possible use as a vital stain, we found its strongest fluorescence is emitted when the source of light has a wave length of 3600 to 3800 Angström units; this is the region of long wave ultraviolet. This deep purple light causes fluorescein to emit a golden or green luminescence depending upon the hydrogen-ion concentration of the media in which the action takes place. In an acid solution the emitted light is yellow; in an alkaline solution it is dull green. To secure the greatest possible contrast, the source of light should exclude nearly all the visible light and all erythema producing ultraviolet. The characteristics of a suitable filter is shown in Figure 1.

Method for Testing the Fastest Circulation Time by Means of Fluorescein. A special, small, inexpensive mercury vapor bulb with a concentrated light beam (Fig. 2) is provided with a purple glass filter which absorbs all the harmful ultraviolet and most of the visible rays.* Of the emitted light 65% is transmitted at the wave length of 3600 Angström units. The beam of this concentrated light is directed against the lips of the patient. The examination should take place, if possible, in a dark room; 5 cc. of a 5% fluorescein solution containing 5% of sodium bicarbonate are injected rapidly by means of a 20 gauge needle into the antecubital vein of the adult patient. Solutions of *sodium* fluorescein in adequate amounts[7,8,11] is optically much less effective and has no advantages over the solution of fluorescein with sodium bicarbonate.† In children 0.7 cc. of solution per 10 kg. of body weight is injected. After the circulation time has passed, the part under observation (lips) suddenly acquires a greenish yellow hue. This end-point is very sharply defined. When several observers are present they rarely disagree by more than 1 second on the moment it appears. If a subsequent examination is intended within a short period, the dose for adults may be cut down to 3 cc. Within 15 minutes the effect has been sufficiently diminished to permit a second examination with a clear cut result.

Normals. Two hundred and sixteen adults from 19 to 96 years of age who never had had any signs of cardiac failure were examined with

* Supplied by the G. W. Gates Company, Franklin Square, L. I.

† Supplied in ampuls by the C. F. Kirk Company, New York.

this method. Great care was taken that all cases were under basal conditions; before the test was made they rested for at least 15 minutes when bedridden, or 30 minutes when ambulatory. However, no fasting

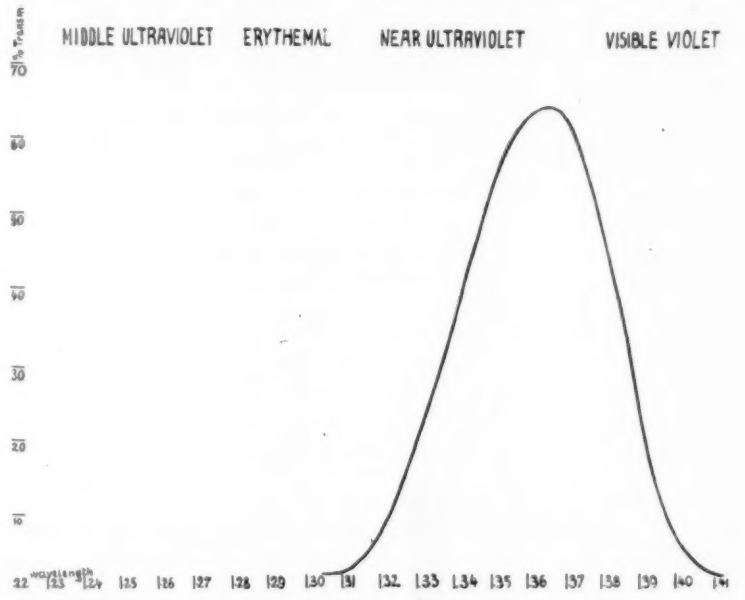

FIG. 1.—Transmission characteristic of the filter as used for the fluorescein observations. A double filter was used in order to decrease transmission of visible light..

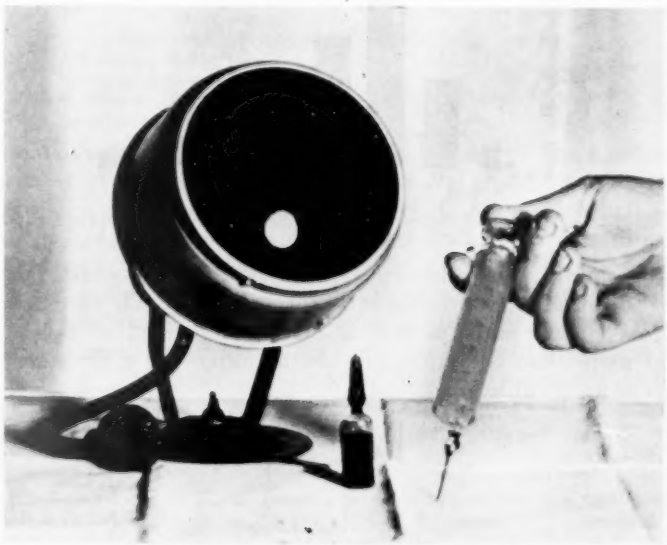

FIG. 2.—Devices needed for the fluorescein test.

was requested. Since many (108) of our patients were elderly, peripheral vascular disease such as arteriosclerosis was not uncommon. In these patients 10 cc. of the fluorescein solution were used in order to observe the status of the peripheral circulation simultaneously. The values ranged almost exclusively between 15 and 20 seconds. The moment at which *full* luminescence appeared in the lips was taken as end-point in all cases. Figure 3 gives the distribution of the values found. It is evident that the great majority of cases ranged around 15 to $17\frac{1}{2}$ seconds; however, if one studies Tables 1 and 2 in which the normals

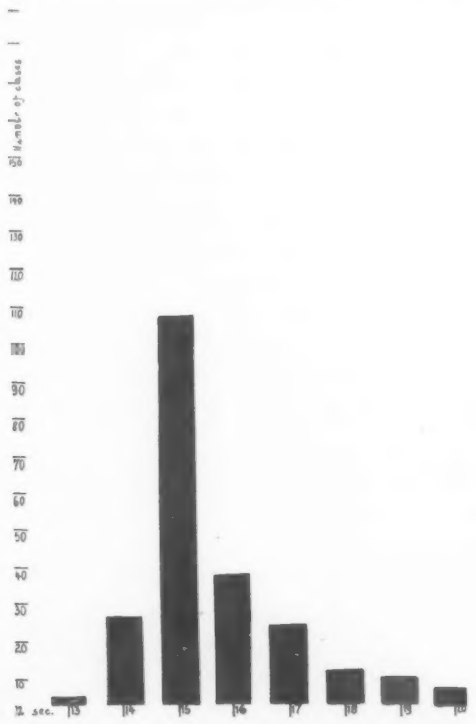

FIG. 3.—Distribution of cases within normal range for circulation time.

are distributed by age, it becomes evident that there is a definite trend toward slower circulation time with increasing age. If repeated tests were done on the same patient at short intervals, the values never differed more than 3 seconds; in the majority the difference was 2 seconds or less (Table 4).

TABLE 1.—CIRCULATION TIME PER AGE GROUP

Age group (yrs.)	No. of cases	Average circulation time (sec.)
20–30	46	15.4
30–40	53	15.8
40–50	61	16.3
50–70	51	17.0
Over 70	5	18.2

Effect of Exercise. Work causes considerable acceleration of the circulation time. The highest value was 6 seconds with maximal exertion of 1350 mkg./min., which could be performed only for a few minutes; this individual had a circulation time of 15 seconds at rest. Moreover, the arm-lip circuit is not the one actually subjected to maximal vasodilatation from exertion; some of its parts may even undergo contraction to make blood available for the working muscle. Therefore this method should not be considered a correct measurement of the relative increase in cardiac output under exertion. The acetylene method, described below, tends to provide an exact impression of the actual average increase in blood velocity under such extreme conditions.

TABLE 2.—DISTRIBUTION OF CASES IN THE DIFFERENT AGE GROUPS ACCORDING TO THEIR CIRCULATION TIME

Circulation time (sec.)	Age group (yrs.) 20–30	30–40	40–50	50–70	Over 70
13–13.9	4				
14–14.9	18	5	2		
15–15.9	18	42	34	11	
16–16.9	4	1	21	9	
17–17.9	0	4	2	16	1
18–18.9	2	1	1	3	3
19–19.9	..	..	..	8	1
20–20.9	..	..	1	4	

Effects of Fever. Six otherwise normal patients were observed during pyrexia due to infectious diseases. The circulation time varied between 9 and 13 seconds whereby no direct relation between the increase in temperature and the percentage of acceleration of blood velocity could be discovered.

TABLE 3.—CIRCULATION TIME

No.	Clinical diagnosis	Arm-conjunctiva	Arm-lips	Arm-rectum	Arm-foot
1	Wound on rt. foot; duodenal ulcer	9	15	19	23
2	Laceration of rt. foot	11	15	20	22
3	Laceration of lt. foot; caisson disease	8	16	21	24
4	Laceration of lt. foot	8	16	20	23

Circulation Time to Different Points of the Body. In 4 patients the fluorescein circulation time was observed at 4 *different points* of the body after the same injections of fluorescein. All patients had a healing open lesion on the foot not due to arteriosclerosis, so that this district could be employed as one point of observation. The second point was the mucosa of the rectum, the third point was the lips, and the fourth the conjunctiva. Four mercury vapor lamps were used; each observer had made many observations previously and was fully acquainted with the method. The results are shown in Table 3. Here again the question arises as to whether the values obtained on the foot and the conjunctiva are more than an approximation of the true blood velocity to these regions.*

* After the conclusion of this paper a photoelectric method was developed to make circulation time determinations to any point of the body. Determinations with this fully automatic method using fluorescein have proved these values correct. In a normal the arm-leg time never exceeds twice the value obtained for the arm-lip time.

Bronchial and Cardiac Asthma. According to Plotz,[16] patients in an attack of pure bronchial asthma show a normal or slightly shortened circulation time. We had the opportunity to observe 5 cases of this kind, and could confirm these results objectively. In contrast to them, 3 cases of pure cardiac asthma (left and no right heart failure) showed a high normal or prolonged circulation time, the extremes being 32 and 20 seconds. Accordingly, the circulation time aids in making the differential diagnosis between these 2 kinds of "asthma" but only if one is dealing with a pure form. In 3 cases bronchial asthma was complicated by beginning heart failure in patients with a known cardiac lesion and slightly prolonged circulation time (22, 23 and 27 seconds) were found. However, prolonged circulation time in a suspected case of bronchial asthma seems to indicate that we are not dealing with a pure case and this fact has considerable importance in the therapeutic program.

TABLE 4.—TESTS REPEATED WITH INTERVALS

No.	Clinical diagnosis	Interval between both tests in min.	Seconds 1st test	Seconds 2d test
1	Decomp. mitral stenosis	60	32	30
2	Decomp. mitral stenosis	85	29	29
3	Decomp. aortic insufficiency	120	29	31
4	Decomp. hypertension	120	40	37
5	Decomp. hypertension	120	29	32
6	Decomp. aortic insufficiency	180	42	45
7	Decomp. mitral stenosis; auric. fibrill.	180	36	31
8	Decomp. hypertension	180	33	33
9	Decomp. aortic insufficiency; auric. fibrill.	180	38	42
10	Decomp. hypertension	180	48	44
11	Myxedema	120	24	24
11*a*	Same case	2 days	23	
		10 days	24	
		17 days	23	
		120 min. after previous test	24	
12	Normal	60	15	16
13	Normal	30	15	14
14	Hyperthyroidism	120	11	10
		1 day	12	
		2 days	10	

Hyperthyroidism. The average circulation time in 42 patients suffering from hyperthyroidism was 10.2 seconds: none of them showed a circulation time of more than 14 seconds and the shortest was 7 seconds. The circulation time seems to be a very sensitive test for hyperthyroidism and, in the absence of cardiac failure, it seems to correspond to the clinical picture much more closely than the basal metabolism rate. The circulation time may remain short after Lugol's solution and after operation even when the basal metabolism has returned to normal. Table 5 illustrates such a case.

Hypothyroidism. Ten cases of hypothyroidism were followed for a long time, and the circulation time was found slightly or markedly prolonged in all except one. The average in this group amounts to 26 seconds. The longest value was 32 seconds. With thyroid medication the values rapidly became normal only to return to slow circulation

times if the administration of thyroid was stopped. It was our impression that changes in circulation time occurred much earlier than changes in the clinical picture.

TABLE 5.—CIRCULATION TIME IN A CASE OF HYPERTHYROIDISM

Day of hospitalization	Treatment	Pulse rate	Basal metabolic rate	Circulation time (sec.)
3	Bed rest	116	+51	7
7	Bed rest	104	+48	8
17	Lugol's, 9 days	90	+32	10
24	Lugol's, 16 days	90	+19	10
25	Subtotal thyroidectomy			
32	Bed rest	96	+ 7	10
46	Out of bed	90	+ 4	11
69	At home	86	+ 4	16
90	At home	90	+ 6	16

Anemia. Twelve cases with anemia of various degrees were observed. Only those cases were included in which there was no other detectable cardiovascular disease. Table 6 seems to indicate that no apparent shortening of the circulation time appears until the red cell count falls to 3,500,000. Below this limit the heart compensated for the loss of oxygen carriers by increasing the speed of blood flow. The number of cases however, is insufficient to state definitely that 3,500,000 cells are tolerated without increase in circulation time.

TABLE 6.—CIRCULATION TIME WITH LOW RED BLOOD COUNT

No.	Clinical diagnosis	Erythrocytes (mill.)	Circulation time (sec.)	Erythrocytes (mill.)	Circulation time (sec.)
1	Pernic. anemia	1.3	9	2.9	12
2	Pernic. anemia	1.6	10	3.4	13
3	Bleeding duodenal ulcer	2.7	12		
4	Bleeding duodenal ulcer	2.6	12		
5	Cancer of stomach	2.5	10	2.3	10
6	Duodenal ulcer	3.0	13	2.4	11
7	Duodenal ulcer	3.2	13		
8	Duodenal ulcer	3.7	15	3.8	15
9	Bleeding hemorrhoids	3.8	16	4.5	16
10	Duodenal ulcer	3.9	15	4.3	16

Comparison Between Fastest and Slowest Circulation Time. To determine whether the fluorescein circulation time by this method is an exact measure of the blood flow in general, recourse was made to a procedure which provides certain information about the slowest flow and also about the average speed of blood flow. Acetylene was first used by Grollman[8a] to determine the stroke volume, but the circulation time can also be found by it. The gas is poorly soluble in the blood lipoids, but it is absorbed by the blood to saturation and can be exactly analyzed by relatively simple methods.

Method. The patient breathes a 6% acetylene-air mixture from a Douglas sack. The expired gas is separated and sufficient amounts are drawn into small rubber bags by Simonson's apparatus. Every 20 seconds a new bag is filled. The samples of gas thus received are then analyzed for their acetylene content. The percentage of acetylene gives the ordinate of a curve, the abscissa of which is represented by the time.

This method, originally devised by Baumann[1] for a different purpose, was used by us with our former collaborator Bielschowsky.[3] It yields information about the time which is required until no, or practically no, acetylene is absorbed by the blood. At this moment all blood has circulated at least once through the lungs. Under basal conditions, the saturation of acetylene in the expired air never fully reaches the values of the inspired gas mixture, since some acetylene diffuses into the tissue and some blood leaks into the rapid circulation from the blood depots. In normal individuals however, the curve becomes absolutely straight after $2\frac{1}{2}$ to $3\frac{1}{4}$ minutes, indicating that all blood in rapid circulation has passed at least once through the lungs. The slowest circulation time was observed in 24 normals in this manner. The same cases were examined with the fluorescein method and the values compared. By the acetylene method, the average for the slowest circulation time was 3 minutes.

Ten cases of thyrotoxicosis were examined the same way, as well as 13 cases of cardiac failure. The patients with thyrotoxicosis needed $1\frac{1}{2}$ to 2 minutes to reach the stabilized phase of the curve, the time varying in accordance with the severity of the disease. The figures obtained with this method agree very closely with those of the fluorescein method for the fastest circulation time.

Patients in cardiac failure had slowest circulation times between 4 and 6 minutes. Table 7 is a comparison between the values found with the fluorescein method for the fastest circulation time and the values found with the acetylene method for the slowest circulation time.

Table 7.—Comparison Between Fluorescein and Acetylene Method in Circulation Times

No.	Name	Fastest circ. time fluorescein (sec.)	Slowest circ. time acetylene (min.)	Remarks
1	Ba	7	$1\frac{1}{4}$	Exercising
2	Sa	10	2	
3	Me	12	2	
4	Scha	13	2	
5	Sto	14	$2\frac{1}{2}$	
6	Ke	18	2	
7	Re	23	3	In failure
8	He	24	3	
9	We	24	$3\frac{1}{2}$	Myxedema
10	Schar.	26	4	In failure
11	Sm	27	$3\frac{1}{2}$	In failure
12	Hi	28	$3\frac{1}{2}$	Myxedema
13	Kn	33	5	In severe failure

The shape of the curve in all our cases was practically identical, so that the average circulation time must have varied in the same proportion. In order to show how a local impairment of the backflow of blood would have influenced such a curve, blood pressure cuffs were applied to the thighs of a patient using subdiastolic pressure to pool blood artificially in these extremities. After the normal lapse of time the acetylene curve reaches its straight level (Fig. 4). This level, however, is considerably lower than the acetylene content of the inhaled air, probably because blood constantly leaks out of the artificially produced blood depots. After the curve becomes straight, the cuffs

were suddenly released. Within a few seconds additional acetylene was absorbed, indicating that blood previously unsaturated now entered the rapid circulation. As expected, the fluorescein circulation time did not show any variation when obtained at the moment of the release of the cuffs.

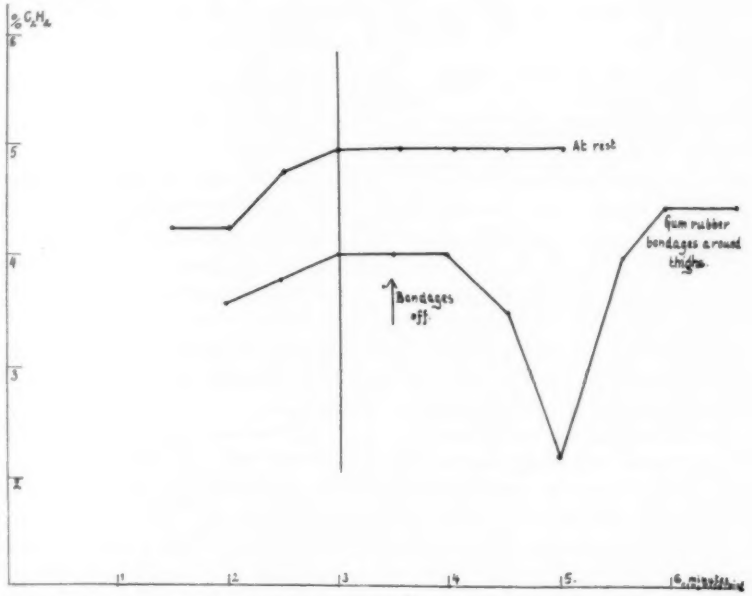

FIG. 4.—Acetylene concentration in the exhaled air of a patient who breathes a 6% acetylene-oxygen mixture. The point when the curve reaches stabilization represents the moment when all blood in rapid circulation has at least once passed the lungs. The lower curve is taken from the same patient with gum rubber bandages around the thighs. After stabilization has been reached the bandages were released. Ordinates: % acetylene. Abscissæ: minutes.

When a patient exercises while breathing the acetylene mixture, the time required for the curve to attain the straight line is very short. Using an exertion of 1200 mkg./min. the slowest circulation time became $1\frac{1}{4}$ minutes, which is approximately $2\frac{1}{2}$ times faster than normal. The fluorescein circulation time in this instance became 7 seconds in comparison to 17 seconds, the basal value for the fastest circulation time of this patient. After reaching the straight level, the expired gas mixture of the exercising patient has practically the same acetylene concentration as the inhaled gas mixture. This suggests that during work nearly all blood depots are used to provide oxygen carriers in the rapid circulation.

Summary. 1. The appearance of fluorescein in the lips under a special long-wave ultraviolet light can be used to determine the circulation time, but certain conditions must be observed in order to obtain reliable results.

2. In 212 normal adults, the values for the fluorescein circulation time ranged between 15 and 20 seconds, the majority between 15 to 17.5 seconds.

3. The average of the circulation time is longer in older patients.

4. Work accelerates the circulation time considerably and may make it 2½ times faster than normal.

5. Fever shortens circulation time (6 cases).

6. The fluorescein method can be used to determine the velocity to different points of the body. The average time to conjunctiva, lips, rectum, foot, is 10, 15, 18 and 23 seconds, respectively. The conjunctiva is not an appropriate place to test the circulation time.

7. In congestive right heart failure 92% of the cases (123 patients) show a prolonged circulation time, while compensated cases of heart disease have normal circulation times.

8. Pure bronchial asthma, having a normal or slightly shortened circulation time, can be differentiated by the fluorescein circulation time from cardiac asthma, which has a prolonged circulation time.

9. Hyperthyroidism is associated with shortened circulation time values, which seems to provide an earlier indication of the clinical situation than the basal metabolic rate.

10. Patients with hypothyroidism have prolonged circulation times.

11. Anemia considerably shortens the circulation time when the red blood cell count goes below 3,500,000.

12. Inhalations of acetylene can be used to determine the time which elapses until all blood in rapid circulation has passed the lungs at least once ("slowest circulation time"). (*a*) Twenty-four normals had the slowest circulation time of 2½ to 3½ minutes. (*b*) Ten cases of thyrotoxicosis showed slowest circulation times of from 1½ to 2 minutes while patients in cardiac failure have slowest circulation times up to 6 minutes. (*c*) Work shortens the slowest circulation time as much as 2½ times the normal. (*d*) The comparative values found with the fluorescein method for the fastest and the acetylene method for the slowest circulation time show the same relation.

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CONGENITAL HEART BLOCK

A Study of Two Cases in Healthy Adults

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Congenital heart block is a rare anomaly; only 80 cases were described up to 1942. It is particularly uncommon to find congenital heart block in adults in the age group presented here.

Case Reports. Case 1. The patient (Mrs. M. S.) is a 20 year old white female who has been seen at intervals for the past 4 years, during which time she has complained chiefly of easy fatigue and weakness.

Past History. The patient was born prematurely after 7 months' gestation. The delivery was normal. Her infancy was normal except for some feeding difficulties; no cyanosis was recorded at any time during infancy or childhood. At the age of 6 the patient was examined by a school physician who reported that she had a very slow pulse rate and a heart murmur. These findings were constant during her school life, but she carried on all activities and participated in all school sports without experiencing any dyspnea, palpitation, syncope or other symptoms of heart disease. She had chicken-pox and measles during childhood, but did not have diphtheria, tuberculosis or rheumatic fever.

Physical Findings. On her first visit in March, 1938, the patient was a thin, white female, height 67 inches, weight 122 pounds. Neither the skin nor the nail beds gave evidence of cyanosis. There was no clubbing of the fingers or toes. The thyroid gland was not enlarged. The apex of the heart was in the 5th interspace, 9 cm. from the mid-sternal line. At the apex, there was a soft, blowing, systolic murmur which occupied the entire systolic phase and was transmitted medially and upward toward the base. The second sound was accentuated; no thrill was palpable. The pulse was 38 and regular. The blood pressure was 100/70. The lungs were clear. The liver and spleen were not palpable. There was no edema of the extremities. There were no congenital deformities.

Laboratory Findings. The urine was negative; blood count normal; Wassermann negative; tuberculin test negative. The basal metabolism was −18%. The roentgenogram of the lungs was normal. Roentgen-ray examination of the heart showed it to be normal in size and shape (Fig. 1). Fluoroscopic examination also revealed no cardiac abnormalities in the antero-posterior, right or left oblique positions. An electrocardiogram showed complete auriculo-ventricular dissociation. There was a 2:1 block present; the auricular rate was 84, while the ventricular rate was 42 (Fig. 2). Both adrenalin (1 to 1000) and atropine sulfate ($\frac{1}{150}$ gr.) were administered separately on several occasions; neither of these drugs changed the pulse rate appreciably nor restored regular sinus rhythm.

Diagnosis. A diagnosis was made of congenital heart disease; complete heart block; and probable interventricular septal defect.

Course. During the past 4 years, the patient has been in good health except for occasional colds. She has worked as a secretary and has been married for the past year. However, she has complained constantly of easy fatigue and weakness. Her pulse has varied between 35 and 45 per minute and has been regular at all times. She has had no attacks of syncope. The basal metabolism has been repeated several times and has ranged between −18% and −8%. The patient has been given several courses of thyroid which made her feel symptomatically better, increased her ability to do things, and helped her gain some weight (15 pounds in 4 years). The thyroid medication never appreciably altered the pulse rate.

CASE 2. The patient (Mrs. C. D.) is a 31 year old white female who has been under medical observation for congenital heart disease ever since birth; yet she has been able to undergo 2 pregnancies, and lives a fairly normal life at the present time.

Past History. The patient was born at term, but was a blue baby at birth and she was considered to have congenital heart disease. At the age of seven months, she was seen by Dr. Charles Gilmore Kerley. At that time she had a loud systolic murmur at the apex and became cyanotic on exertion.* At the age of 3, she had an illness which was considered to be poliomyelitis. She wore braces on her lower legs for 2 years following this, and has enjoyed normal function of her extremities since that time. When she was 9 years old, an

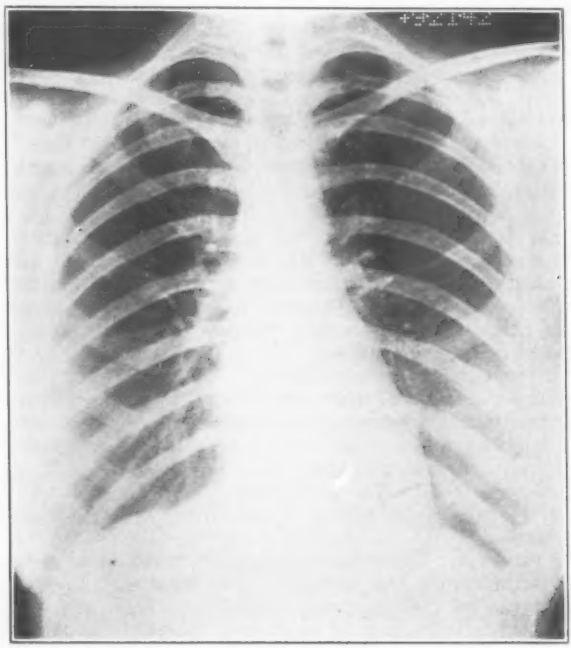

FIG. 1.—M. S. Heart size and shape are essentially normal.

electrocardiogram showed the presence of complete heart block which was felt to be truly congenital in origin. In 1924, she came under the care of Dr. Harold E. B. Pardee who felt that the history together with the electrocardiographic evidence predicated the diagnosis of congenital heart block. In 1927, she was seen by one of us and a tracing was made (Fig. 3). This showed complete auriculo-ventricular block.

Physical Findings. In 1927, the patient was a thin, white female of 17. There was no cyanosis and no clubbing of the fingers or toes. The apex impulse was in the 5th interspace, well inside the mid-clavicular line. She had a harsh, blowing, systolic murmur which was heard loudest at the 2d and 3d left intercostal spaces and was transmitted upward. The pulse rate was 35; the blood pressure was 90/60. The lungs were clear; the liver and spleen were not palpable. There was no edema of the extremities.

Laboratory Findings. The urine was negative; blood count essentially normal. The Wassermann and tuberculin tests were negative. An orthodia-

* Personal communication from Dr. Kerley.

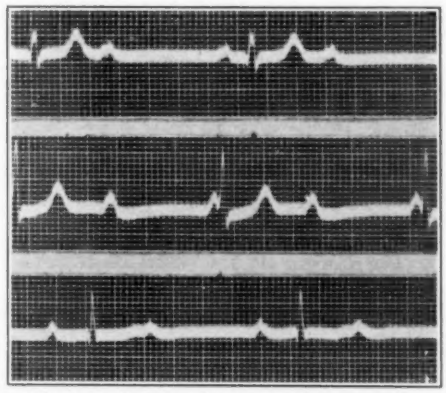

FIG. 2.—M. S. Electrocardiogram shows complete auriculo-ventricular block.

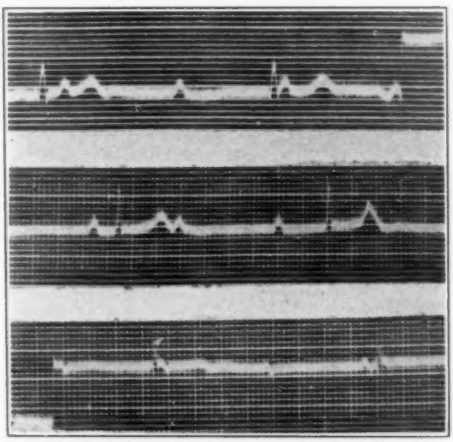

FIG. 3. C. D. Electrocardiogram taken in 1927 shows complete heart block.

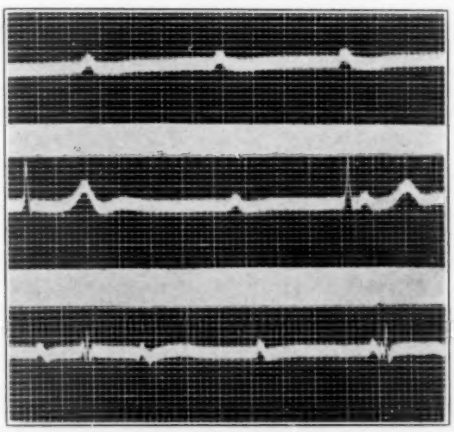

FIG. 4.—C. D. Electrocardiogram taken in 1941. This tracing is almost identical with the one taken in 1927 (Fig. 3).

graphic tracing gave a measurement of 13.5 cm. for the transverse diameter of the heart. An electrocardiogram showed complete auriculo-ventricular block. The auricular rate was 75, while the ventricular rate was 35.

Diagnosis. A diagnosis was made of congenital heart disease; complete heart block; and probable interventricular septal defect.

Course. Under Dr. Pardee's supervision, the patient has undergone two pregnancies successfully. During the last quarter of the first pregnancy (in 1935), she experienced some dyspnea. During delivery her pulse rate gradually increased and at one point was 68 per minute. This increase in rate was due to the appearance of premature beats which started about an hour before delivery. Her pulse rate dropped back to 44 15 hours after delivery. Her respiratory rate increased to 32 per minute before delivery, but decreased to 23 6 hours thereafter and did not rise again. She had a slow but uneventful convalescence. The second pregnancy came in 1938. This delivery was short and uneventful; there was no rise of pulse or respiratory rate of any significance. In December 1940, when she was under considerable strain because of illness in the family, she had several fainting spells which sounded like Stokes-Adams seizures. However, no observation was made on her during these attacks. An electrocardiogram taken by Dr. Pardee in 1941 shows that complete A–V block is still present (Fig. 4).* At the present time the patient is well and able to carry on the usual activities of taking care of her home and 2 children without discomfort of any sort.

Comment. Both these patients have lived fairly normal lives in spite of the fact that they have complete heart block of congenital origin. Mrs. C. S. is not only in an age group seldom reported with congenital block, but she has also carried two pregnancies through to term.

According to Yater,[5] heart block of congenital origin is distinguished by the following conditions: (1) An electrocardiogram which shows complete block. (2) A slow pulse that has been noticed at an early age and has continued to be present. (3) The absence of any history suggestive of an infection that might produce block; these infections are diphtheria, tuberculosis, syphilis and rheumatic fever. (4) Syncopal attacks. (5) The presence of a congenital heart lesion; usually a patent interventricular septum.

Both patients presented herewith have electrocardiographic evidence of block. Mrs. M. S. has had a slow pulse from childhood; Mrs. C. D. was considered to have congenital heart disease from birth and has had *electrocardiographic evidence of heart block since the age of 9.* Neither of the patients has a history nor laboratory findings which would indicate an infection as the cause of the block.

Mrs. M. S. has never had syncopal attacks, but Mrs. C. D. has had several fainting spells. Since the latter's pulse rate often dropped below 30 (Fig. 4) the basis for the syncope is evident. The electrocardiogram of both cases showed normal ventricular complexes. Leech[4] points out that when this occurs the block must be in the course of the main bundle of His above the bifurcation.

Both patients possess rough, low-pitched, systolic murmurs heard loudest in the 2d and 3d interspaces. Due to the character and location of these murmurs, it has been assumed that they are caused by an interventricular septal defect. According to Wallgren and Win-

* We wish to express our appreciation to Dr. Harold E. B. Pardee for furnishing this data and permitting us to use it.

blad[4] 66% of the reported cases of congenital heart block have this anomaly. Only 11 of the reported cases have come to autopsy. Six of these showed interventricular septal defects; 2 had a patent ostium primum; 3 had intact septa. These findings would seem to indicate that interruptions in the conduction system are not necessarily associated with septal defects but may be independent malformations. Septal defects are the commonest congenital cardiac anomalies (Abbott[1]) yet congenital heart block is rare. Fleming and Stevenson[2] believe that this is due to the fact that the usual septal defects are anterior to the pars membranacea while the main bundle of His lies behind it.

Complete congenital heart block is not in itself fatal. The cases presented herewith give further evidence that it is possible for a person with this anomaly to reach adult life without serious cardiac symptoms.

Summary. Two cases of congenital heart block are reported. The first case, which has been studied for 4 years, is a healthy adult who has no cardiac symptoms and no other apparent anomalies. The second case, which has been followed from birth, has had no cardiac symptoms except for some syncopal attacks. This case is of particular interest in that the patient has had two normal pregnancies without any serious cardiac disturbance.

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SYPHILITIC ANEURYSM OF CELIAC ARTERY

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Aneurysms of the celiac artery are rare, but somewhat less so than is true of the branches of this artery. A moderate number of reports of celiac aneurysms has appeared in the world's literature, but the descriptions are often so brief and in some instances so obviously inaccurate that the exact situation and etiology are obscure. Thirty-two of the reported cases can be accepted as true aneurysms of the celiac artery, all having been proven by autopsy. Seven of these (Archer,[1] Aronssohn,[2] Baccelli,[3] Bergeon,[9] Concato,[12] Maunsell,[31] Omodei-Zorini[32]) were probably due to syphilis. In 21 (Balme-Dugarray,[4] Bartholow,[5] Baynham,[7] Bruen,[10] Cleveland,[11] Cutler[13] [2 cases], Dowse,[14] Federici,[15] Graziadei,[19] Heitz,[20] Holmes,[21] King-Fretz,[23] Klob,[24] LeVay,[26] Lewis,[27] Lieutand,[28] Lyman,[29] McCarthy,[30] Panizza,[33] Solis-Cohen[36]) the etiology was either unknown or not stated. In 3 instances (Gorham,[18] Omodei-Zorini,[32] Sas[34]) the possibility of trauma being the

responsible factor was worthy of consideration. In the curious case described by Kolisko[25] the finding of a hog bristle in the aneurysmal wall suggests that the patient might have swallowed the bristle which had lodged in the aneurysm after passing through the wall of the intestine. At that time the bakers of Vienna used hog bristle brushes in making bread.

The first case confirmed by autopsy was described by Bergeon in 1830. The patient had general paresis and the aneurysm of the celiac artery was presumably syphilitic.

In 1862, Concato[12] described a typical aneurysm of the celiac artery which was diagnosed in life. The patient was a 38 year old male who had syphilis, epigastric pain, fever and a pulsating abdominal tumor mass. Autopsy revealed a ruptured saccular aneurysm of the celiac artery.

The last recorded case (1941, LeVay) was that of a 58 year old white female who had signs and symptoms of acute cholecystitis—vague gastro-intestinal symptoms for some 6 months, then sudden severe epigastric pain radiating to the right shoulder, nausea, slight icterus and fever. There were signs of localized peritonitis and a palpable mass in the right upper quadrant. The patient died suddenly 6 days later. Autopsy revealed an aneurysm of the celiac artery which had ruptured into the lesser peritoneal cavity. Death was due to pulmonary embolism arising from a thrombus in the compressed inferior vena cava. The pain in the shoulder and icterus were thought to be due to pressure on the diaphragm and bile ducts respectively. There was no evidence of syphilis and there was very little arteriosclerosis. Other cases are indicated in the bibliography at the end of this paper.

Three cases (Battaglia,[6] Smith,[35] Soós[37]) of false or spurious aneurysm of the celiac artery, tuberculous in origin, have been reported. In all 3, caseous tuberculosis of the regional lymph nodes evidently had extended to the celiac artery, resulting in tuberculous arteritis and aneurysm formation.

A fourth case of spurious aneurysm of the celiac artery was reported by Irvine.[22] The patient had nephrolithiasis, pyelonephritis and extensive suppuration of the retroperitoneal tissues. The extension of the acute inflammatory process to the celiac artery resulted in destruction of its wall and localized dilatation.

In the case to be reported, the aneurysm was due to syphilis. It is the only instance of aneurysm of the celiac artery in 8070 autopsies performed at the Institute of Pathology of Western Reserve University and University Hospitals.

Case Report. A negro, aged 44, was first admitted to the hospital December 29, 1941. His chief complaint was constant epigastric pain which radiated laterally along both costal margins. He had had similar epigastric pain, intermittent in character, for over 3 years.

Physical Examination. Temperature 37.4° C., pulse 96, respirations 22, blood pressure 160/114. The heart was slightly enlarged to the left and there were systolic and diastolic apical murmurs. In the left upper quadrant of the abdomen there was a pulsating, firm, tender, fixed mass, measuring about

6 cm. in diameter. Roentgen ray and fluoroscopic examination revealed an enlarged left ventricle, slight dilatation of the ascending aorta, and calcareous deposits in the abdominal mass. The blood Kline exclusion test was negative.

At this time the most probable diagnosis was thought to be syphilitic aortitis with aortic insufficiency and aneurysm of abdominal aorta. He was discharged

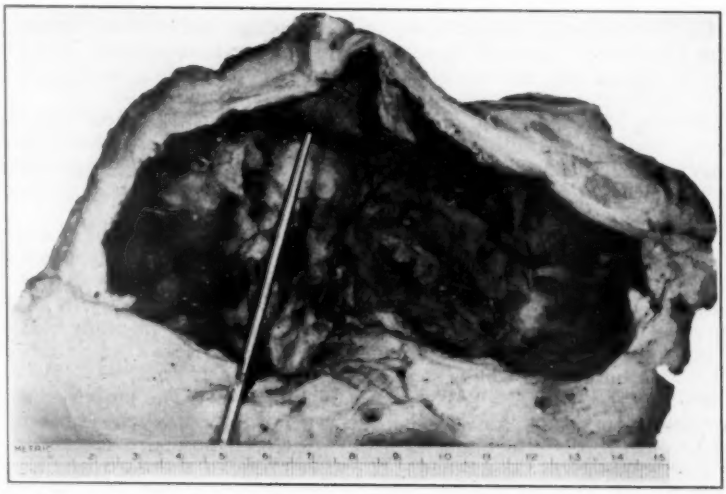

FIG. 1.—Photograph of the aneurysm, including a portion of the aorta. The probe lies in the lumen of the aneurysm and continues in the lumen of the celiac artery.

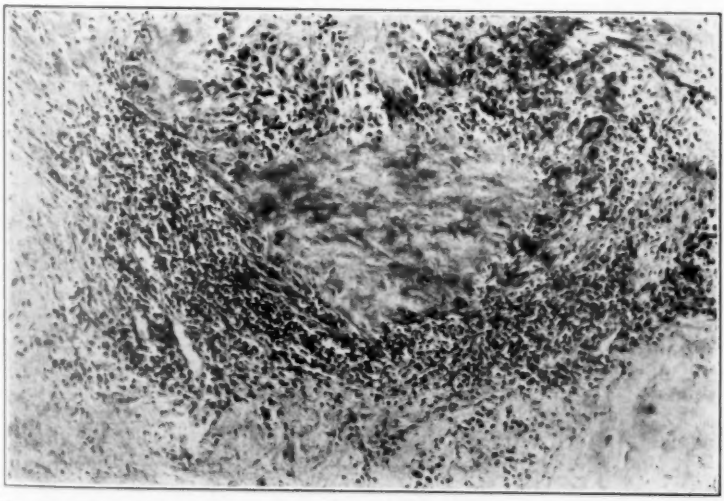

FIG. 2.—Photomicrograph of the aorta showing miliary gumma in media. × 165.

after 5 days and subsequently visited the dispensary regularly. The epigastric pain persisted but was sufficiently relieved with analgesics to enable him to work as a garbage collector for 3½ months. In the latter part of April, 1942, he noticed increasing weakness, generalized muscular soreness, shortness of breath on exertion, and at night frequently had chills, fever and night sweats.

Two weeks before readmission to the hospital he first noticed swelling of the ankles and 10 days later vomited some clotted blood. From this time on his stools are said to have contained bright red blood.

He was readmitted on May 30, 1942.

Physical Examination. Temperature 40.1° C., pulse 96, respirations 20, blood pressure 140 70. There was slight pallor and slight generalized icterus. The pupils did not react to light. There was no noteworthy change in the heart. The pulsating tender abdominal mass was still present, measuring about 7 cm. in its greatest diameter. The liver extended 2 cm. below the costal margin in the right midclavicular line and was slightly tender. There was marked cutaneous hyperesthesia over the abdominal mass.

Laboratory Reports (day of admission). Urine: sp. gr. 1.015; contained bile pigment and a few white blood cells, no casts, albumin and sugar negative. Blood: 24,000 WBC (85% neutrophils, 12% lymphocytes, 3% monocytes), 2.5 mill. RBC, 45% Hgb. (Sahli); negative Kline exclusion test; icterus index 19.

Hospital Course. The patient continued to pass blood by rectum and his hemoglobin gradually fell, in spite of 3 transfusions of whole blood totaling 1600 cc., to 28% on his 16th hospital day. The icterus index rose to 30 by his 17th hospital day. He had a continued spiking temperature with a maximum of 39° to 40° C. in the late evening. At times he was mentally confused and irrational. On his 18th hospital day he vomited a large amount of bright red blood, soon became comatose and died shortly thereafter.

Autopsy (No. 7804 by Dr. W. B. Chamberlin, Jr.). The most significant observation was a syphilitic saccular aneurysm of the celiac artery measuring 15 x 7 x 4 cm. All of the branches of this vessel were normal. The aneurysm was approximately in the midline. It had compressed and destroyed a large portion of the head of the pancreas. There was a direct communication between the main pancreatic duct and aneurysmal sac. Clotted blood was present in the distal 3 cm. of the pancreatic duct and projected from the ampulla of Vater. There was also considerable clotted blood throughout the gastro-intestinal tract. In its proximal two-thirds, the pancreatic duct was distinctly dilated and there was moderate fibrosis of the entire pancreas. The aneurysm had also displaced, compressed and partially obstructed the second portion of the duodenum and common bile duct. The extrahepatic and intrahepatic bile ducts were markedly dilated and there was ascending acute cholangitis with multiple small abscesses in the liver. Generalized icterus of moderate degree was present with an associated cholemic nephrosis. Indisputable gross and microscopic stigmata of syphilis were present in the thoracic and abdominal portions of the aorta. There was also syphilitic valvulitis and slight insufficiency of the aortic valve. No spirochetes could be found in the aorta or aneurysmal wall, but a miliary gumma was demonstrated in the aortic arch. The inner surface of the aneurysm showed numerous large projecting pale bluish-gray, translucent, hyalinized intimal plaques. There were few atheromatous masses and there was little calcification. Within and between the projecting intimal plaques there was retraction of intima producing stellate and parallel depressed lines. These gross findings are typical of syphilitic arteritis.

Comment. Both clinically and pathologically the case reported is unusual. Generalized icterus and bleeding from the gastro-intestinal tract are uncommon clinical manifestations of abdominal aneurysms. Jaundice is particularly rare. The celiac artery and one of its branches, the hepatic artery, are in close proximity to the extrahepatic bile ducts, a relationship which makes compression and obstruction of the bile ducts by aneurysm of these vessels a likelihood, with consequent generalized icterus. It is worthy of note that in such cases the signs and symptoms may simulate acute cholecystitis or primary hepatic disease.

Hemorrhage into the gastro-intestinal tract in patients with aneurysms of large vessels is usually due to erosion of esophagus, stomach or intestine and rupture of the aneurysmal sac into the lumen of one of these viscera. In this case there was erosion of and rupture into the main pancreatic duct with hemorrhage into the gastro-intestinal tract by way of the ampulla of Vater.

The rarity of the situation of the aneurysm in this case is indicated by the fact that only 32 acceptable cases of aneurysm of the celiac artery are found in the literature. In all but 2 cases, death resulted from rupture of the aneurysm and hemorrhage into the peritoneal cavity or retroperitoneal tissues. In 3 cases syphilitic arteritis was established as the cause. In most instances the etiology was unknown or not stated. The majority of the cases, however, were reported before 1895, when Döhle first established the relationship between mesaortitis and syphilis. It is, therefore, probable that many considered to be of unknown cause were syphilitic. False aneurysms of this artery occasionally result from tuberculosis, acute suppurative inflammation and possibly trauma.

Miliary gummas are not commonly demonstrated in chronic syphilitic aortitis. Gordon, Parker and Weiss[17] found microscopic gummas in 8 of 360 cases, an incidence of 2.2%.

Summary. Review of the literature shows that aneurysm of the celiac artery is rare. The case reported is one of saccular syphilitic aneurysm of the celiac artery complicated by bleeding into the intestinal canal by way of the pancreatic duct. The signs and symptoms simulated acute cholecystitis.

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LOCALIZED AGNOTOGENIC (OF UNKNOWN ORIGIN) XANTHOMATOSIS OF SPLEEN WITH SPLENOMEGALY AND ANEMIA

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The formulation of a rational basis of classification for the lipoidoses has been made possible in recent years by the chemical isolation of the specific substances accumulated and deposited during the course of the disease. The chemical structure of these substances, their interrelationship and pathologic significance are indicated in Figure 1.

Thus, the chemical nature of the accumulated lipoid determines the classification. It is recognized, however, that other related lipoids may also be present in quantities above normal.

Further subdivisions may be made and are desirable according to the organ or organs involved and the clinical course.

At present, the following clinical forms are recognized:*

A. Cerebroside lipoidosis: Morbus Gaucher: (*a*) infantile form; (*b*) adult form.

B. Phosphatide lipoidosis: (*a*) Niemann-Pick's disease; (*b*) amaurotic familial idiocy.

C. Xanthomatosis or cholesterol lipoidosis: I. Idiopathic: (*a*) acute: Letterer-Siwe's disease; (*b*) chronic: (1) Hand-Schueller-Christian's syndrome; (2) cutaneous: disseminate and tuberous form; (3) cerebral; (4) pulmonary; (5) cardiovascular; (6) hepatic; (7) osseous; (8) splenic.

II. Secondary: (1) diabetic; (2) icteric; (3) nephritic; (4) dietary; (5) experimental.

In most instances, the visceral xanthomatoses are combined with one or the other type of cutaneous lesion. According to Thannhauser and Magendantz,[27b] a definite correlation exists between the type of cutaneous lesion and the localization in the viscera. Thus, it would be possible to predict from the character of the xanthomatous skin lesion, the organ involved in a similar process.

* Comprehensive discussions of the lipoidoses may be found in the articles and monographs of Buerger,[4] Epstein,[8] Jaffé,[12] Pick,[18] Rowland,[21] Thannhauser.[27]

The various forms of essentially visceral xanthomatosis form a residual group.[18] Only the syndrome of Hand-Schueller-Christian has received consideration comparable to that given to Gaucher's and Niemann-Pick's disease. The other types are not well known, particularly as there are only few chemical data available.[9,13,25] Xanthomatosis envolving primarily the brain has been described by Bogaert and Scherer[3] together with Epstein and Lorenz[8a]. Primary palmonary xanthomatosis has been discussed by Noethen.[17] Recently, Mueller,[16] and Bloom, Kaufman and Stevens[1] published several cases of familial xanthomatosis of the skin and emphasized the rôle of familial xanthomatosis in hereditary heart disease. Cases with xantho-

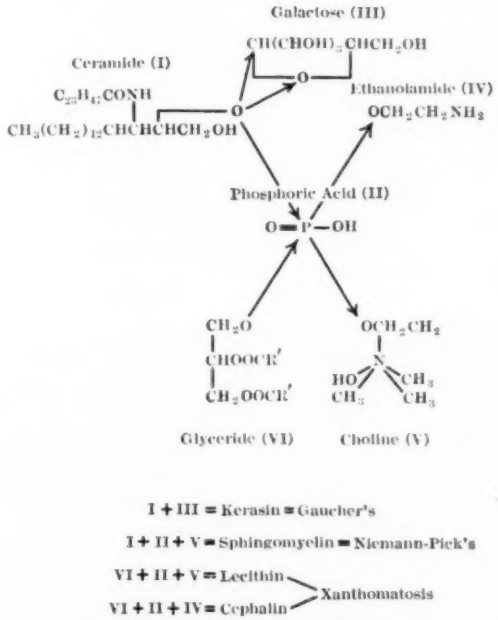
Galactose (III)
Ceramide (I)
Ethanolamide (IV)
Phosphoric Acid (II)
Glyceride (VI)
Choline (V)
I + III = Kerasin = Gaucher's
I + II + V = Sphingomyelin = Niemann-Pick's
VI + II + V = Lecithin
VI + II + IV = Cephalin
Xanthomatosis

FIG. 1.—Chemical interrelationship of the substances deposited in the principal clinical forms of lipoidosis.

matosis of the biliary system have been investigated by Buerger,[4] Thannhauser,[27a,b] and others. Xanthomatosis of the bones has been described by Chester.[5]

All these localized forms of xanthomatosis encroach upon the function of the organ involved. We have had occasion to study a case of primary xanthomatosis of the spleen with splenomegaly and anemia as the main clinical symptoms. This anemia disappeared after splenectomy. We have not found a similar case in the literature.

Case Report. Nancy C., white, aged 6, of English-Scottish stock, was born, at term, from healthy parents. She weighed 8½ pounds. She had measles but none of the other infectious diseases of childhood. She used to have frequent attacks of tonsillitis which stopped after a tonsillectomy was

performed when she was 5 years old. However, since that time, she was not well, tired easily, became pale and developed *café au lait* colored spots and blotches on the trunk, face and thighs. She had never been very strong and her appetite was always poor. When she was 1 year old, she had an attack of vomiting, fever and epigastric pain which lasted several days. As an infant, she had fainting spells after "holding her breath." Since then, and up to the present time, she used to wake up in the middle of the night feeling faint and being confused, sometimes vomit and wet her bed. Such episodes occurred at intervals of 4 to 6 weeks. Similar attacks occurred occasionally after exertion. No such attack was ever witnessed by a physician. Her sleep was always very light. Her mental development was normal and she did very well in school.

Her local physician found her anemic (no data available) and gave her appropriate doses of iron and liver extract without any improvement in the anemia which was said to have been moderate. She then was seen in consultation by Dr. M. M. Fliess* who noticed a marked enlargement of the spleen and found her red count between 3.5 and 4 M c.mm. The medical treatment was continued for a while but without result. She was then referred to the Chesapeake & Ohio Hospital, Clifton Forge, Va., for further study.

On admission (3–12–41), she did not appear acutely ill. She was a delicate, well-developed and fairly well-nourished child. Her skin was of fine texture, moist, pale, with irregular *café au lait* blotches on both sides of the thorax, on one cheek, on both thighs and arms. There was no thickening of the skin and no induration. The spleen was palpable 3 fingers below the ribs. It seemed smooth and firm. No lymph nodes were palpable. The mucous membranes were pale. Otherwise the physical examination was entirely negative. Temperature, pulse and respiration were normal.

Laboratory Tests. Urine: no abnormal constituents. Blood: red cells, 3,145,000; hemoglobin, 64% (Hellige); color index, 0.94; volume index, 1.1; slight anisocytosis; no sickle cells, no spherocytes, no nucleated red cells; white cells, 5100 (segmented neutrophils 50%, stabs 5%, monocytes 3%, eosinophils 2%, lymphocytes 40%); platelets, 180,000; bone marrow: normal composition, no abnormal cells; bleeding time, 4 minutes; coagulation time, 4½ minutes; fragility of red cells: partial hemolysis at 0.44% NaCl, complete hemolysis at 0.34% NaCl; icterus index, 4.6; bilirubin, less than 2.5 mg. per 100 cc; blood cholesterol, 125 mg. per 100 cc; blood urea, not determined; Exton Rose glucose tolerance test (at a later date—6–17–42): 124.2, 99, 82 mg. per 100 cc; blood pressure, 100 systolic, 65 diastolic.

Roentgenographic Studies. The pituitary fossa was normal in size and regular in outline. No lesions of the bony skull, the ribs and the extremities were noted. The lung fields were clear.

In view of the splenic enlargement and leukopenic anemia which had proved absolutely refractory, it was decided to perform an exploratory laparotomy with possible removal of the spleen. The possibility of a lipoidosis was considered but the absence of abnormal cells in the bone marrow and negative roentgenologic findings seemed to speak against this diagnosis.

Operation: The spleen was removed in the usual manner after separating some adhesions. Inspection of the abdominal organs, especially the liver, showed none of them unusual. The postoperative course was uneventful. Four days after operation the blood count was: red cells, 4,550,000; white cells, 16,700 (segmented neutrophils 71%, stabs 13%, monocytes 4%, eosinophils 0%, lymphocytes 12%); platelets, 273,000.

She was discharged 10 days after operation. Unfortunately, no close follow-up was possible. She was seen, however, once again, 14 months later. She had gained weight and grown normally. The brownish areas on her skin were still present but to a lesser degree. She still had the occasional attacks as described above. Otherwise she seemed to do well. Her blood count was: red cells, 4,440,000; hemoglobin, 96% (Hellige); color index, 1.05; white cells, 13,500 (segmented neutrophils 27%, stabs 3%, monocytes 4%, eosinophils 2%,

* Dr. M. M. Fliess, Clifton Forge, Va., furnished the clinical data.

lymphocytes 64%); platelets, 501,000. Her urine was normal. The blood cholesterol was 130 mg. per 100 cc.

On June 22, 1943, the patient seemed well and has made adequate progress physically and mentally. There were a number of small firm lymph nodes palpable in the neck, in the axillæ and in the groin. They were not tender. I suppose they formed after removal of the spleen. A Roentgen ray of the skull was normal. The urine showed no abnormal findings. Hemoglobin was 89.1% (Hellige). Red cells, 4.43 million c.mm. White cells, 10,050 (69%

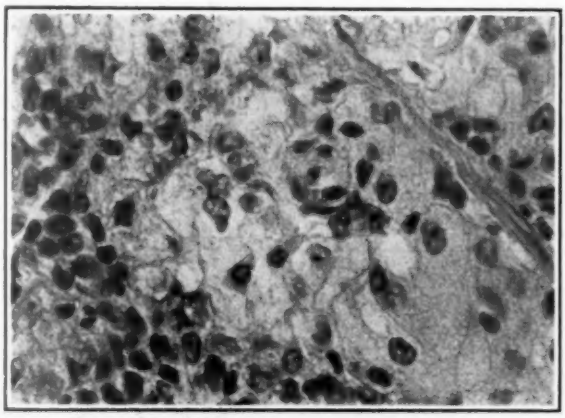

FIG. 2.—Foam cells in splenic pulp. Stain: H. and E. × 670.

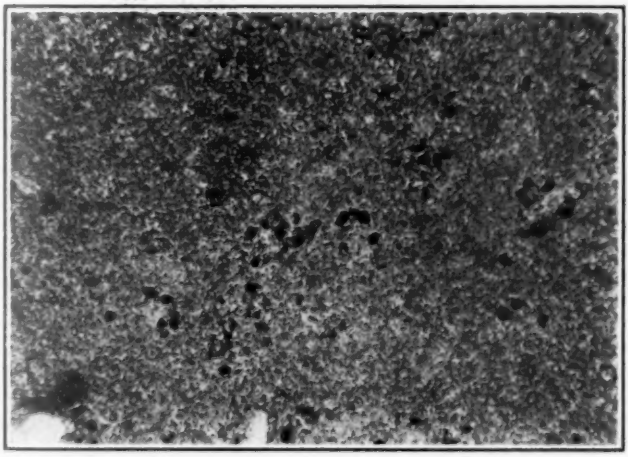

FIG. 3.—Sudanophil matter in droplet form (black in photograph). × 80.

lymphocytes, 1% monocyte, 2% neutrophil stabs, 34% neutrophils segmented and 1% eosinophil). The platelets were 886,000. The hematocrit was 41. Bleeding time, 4 minutes; coagulation time, 4½ minutes. Urea nitrogen, 10 mg. per 100 cc. Blood calcium, 10.4 mg. per 100 cc. Blood phosphorus, 4.5 mg. per 100 cc. Cholesterol, 220 mg. per 100 cc. Glucose tolerance test, 5 hours: 105, 116, 98, 74, 90, 86 mg. per 100 cc.

The value for cholesterol which is now high normal contrary to the low normal on previous occasions is noteworthy.

DESCRIPTION OF THE SPLEEN. The spleen was enlarged to about 3 times its normal size. It weighed 190 gm. and was firm. The margins were rounded. The capsule was thin except for a few fibrous adhesions. The vessels were normal. The cut section was dry, dull brick red with numerous grayish miliary nodules. Sections were stained with hematoxylin-eosin, trichrome (Foot), elastica, Sudan 4, and impregnated with silver (Foot).

Microscopic Findings. The follicles were placed far apart due to the marked hyperplasia of the pulp. The reticulum cells of the pulp were large. In paraffin sections, their protoplasm was clear and foamy (Fig. 2). The nuclei were small, dark staining and located centrally or somewhat to the periphery of the cell. With Sudan 4, the protoplasm appeared to contain orange red droplets or fine gold brown dusty granules; frequently it was Sudan-negative (Fig. 3). The foam cells formed heaps and strands which filled the major part of the pulp. They were less numerous around the follicles (Fig. 4). The sinuses were compressed and almost bloodless. Their endothelium was flat and did not contain lipoid. In the perifollicular areas, where the lipoid-containing cells were less numerous, the sinuses were congested. Fat was also found in the reticulum cells of the germinal centers, in perivascular histiocytes

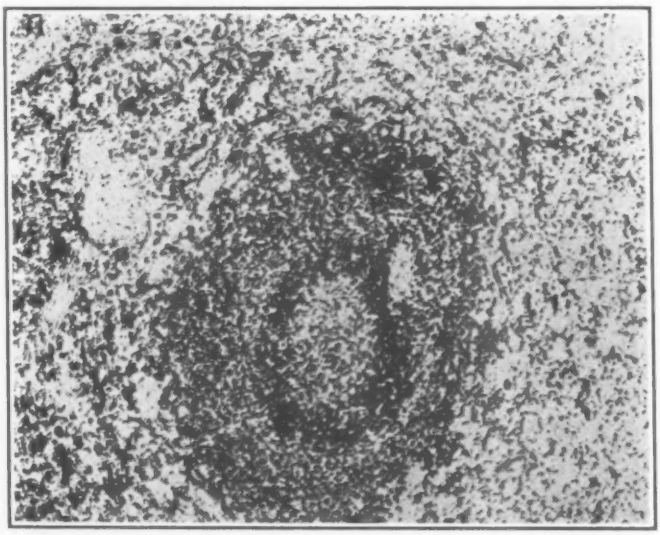

FIG. 4.—The xanthomatous process is less marked around the follicles. The clear zones are areas filled with foam cells. × 108.

of the Malpighian arteries and of the trabecular vessels. There was no inflammatory reaction. There was no fibrosis. No giant cells were seen.*

CHEMICAL ANALYSIS OF THE SPLEEN. The spleen after 2 days in Kaiserling Nr. 1, was washed carefully and placed in 10% formalin. The quantitative analysis was started a few days later.

* In this connection, we have recently had a case (Univ. of Penna. Hosp., Aut. '42-1280) of splenic lipoidosis which would probably be allocated as "secondary" in the classification below. The patient, a 19 year old colored girl with a patent foramen ovale and mild pulmonary stenosis, developed subacute glomerulonephritis with the nephrotic syndrome and lost serum proteins until her A/G ratio was 1.2/1.7 gm. She had a persistent hypercholesterolemia reaching 780 mg. per 100 cc.; Hb, 6.6 gm.; and normal W.B.C. counts. At autopsy, her spleen (weight 550 gm.) was smooth, homogeneous, dull pink, flabby with bulging cut surface. Histologic examination revealed numerous, often coalescent collections of large cells 40 to 120 micra in diameter, with

The lipoids were extracted with alcohol and ether (Bloor[2]) and isolated in petroleum ether. The phosphatides were precipitated from the petroleum ether with acetone and magnesium chloride. The lecithin and cephalin were then dissolved in ether. The lecithin was determined from its cholin content by the method of Roman[19] as modified by Kirk.[15] The diaminophosphatide was then estimated by the method of Thannhauser and Setz[27b] by precipitation with Reinecke acid. Cephalin was estimated by difference. The cerebrosides, which were present only in traces, were determined by the method of Kimmelstiel[14] as modified by Kirk.[15]

The values are expressed in mg. per 100 gm. of dry weight.

For comparison, the values of splenic lipoids in other types of lipoidosis are also tabulated:

	Dreyfuss Fishberg	Normal	Niemann-Pick	Gaucher	Tay-Sachs
Total cholesterol	6.36	0.6– 2.3	6.73	2.72	2.67
Free cholesterol	3.12	0.5– 1.1	6.70	0.52	1.00
Ester cholesterol	2.20	0.2– 1.2	0.03	2.20	1.67
Total phospholipids	18.30	5.5–11.0	42.50	9.39	6.58
Lecithin	10.24	3.1– 4.0	...	7.34	4.44
Cephalin	7.11	1.6– 4.0	...	1.50	1.23
Fatty acids	7.83	7– 9	...	6.10	7.25
Sphingomyelin	0.95	0.7– 1.0	32.70	0.55	0.91
Cerebrosides	traces	traces	...	6.65	

Comment. The outstanding feature of this case was a splenic enlargement caused by accumulation of lipoid substances in the reticulum cells of the spleen. As established by quantitative chemical analysis, the increase of lipoids was mainly in the monaminophospholipids: lecithin and cephalin. The total cholesterol was also increased from 3 to 10 times normal. The ratios between total cholesterol, ester cholesterol and free cholesterol were not markedly changed. The phospholipids were increased due to the high values of lecithin and cephalin. Sphingomyelin was present in normal amounts and thus the possibility of Niemann-Pick's disease could be discarded. The cerebrosides were found to be present only in traces and therefore Gaucher's disease was also ruled out. Accumulation of cholesterol and monoaminophospholipids, on the other hand, is characteristic for xanthomatosis, essential or secondary. The total cholesterol of the blood was low normal. The significance of this fact will be discussed later.

The chemical results fit with the histologic findings. The appearance of the protoplasm was definitely not that of the Gaucher cell. A large proportion of the lipoid-containing cells was Sudan-positive, with variation of degree. No special staining methods for lipoids were applied because it was felt that they were not very reliable. There was no double refraction, a fact for which we have no explanation. The fatty substances were present only in the reticulum cells, prevalently in the pulp but also in the Malpighian follicles and in

1 to 5 nuclei and pale pink, staining, somewhat vacuolated or rarefied cytoplasm, containing no sudanophilic nor anisotropic material. These cells were all in the pulp and extrafollicular. Elsewhere this change was found only in a few lymph nodes. The renal tubules had moderate amounts of sudanophilic material and small amounts of anisotropic substance, and the hepatic cells contained finely divided, evenly distributed droplets which stained partially with Sudan IV. We have tentatively classified this case as xanthomatosis of the spleen and lymph nodes, associated with hypercholesterolemia.—EDITOR.

perivascular histiocytes. The endothelium of the sinuses did not participate at all in the process. This fact has previously been emphasized by Pick.[18] Fat is normally present in the spleen in small amount, mainly in the reticulum cells of the follicles. It may be considerably increased experimentally by oral or intravenous introduction of cholesterol or sphingomyelin.[10]

Lipoid-containing cells have been found in the spleen in cases of severe diabetes and in cases with diabetic lipemia. Usually, this does not cause splenic enlargement. In a small number of cases, however, a splenic tumor was present. Schultze[24] was the first to describe lipoid cell hyperplasia of the spleen in diabetes. A number of other reports followed. A certain distinction has been made between the splenic xanthomatosis associated with diabetic xanthelasma and that of diabetic lipemia. It has been claimed that in the latter, because of its more acute course, the character of the intracellular lipoids is more variable than in the former and the picture more marked. Except for the chemical analyses carried out in the cases of Fahr and Stamm[9] and Siegmund,[25] the interpretation of these cases is based solely on histochemic reactions. It seems probable that the underlying mechanism is the same in all of them and the variations do not warrant a separation into two groups.

Xanthomatosis of the spleen in non-diabetic patients has been reported by Dyke[7] and Wille-Baumkauff.[31] Dyke found the characteristic splenic lesions in a patient with cirrhosis of the liver, pancreatitis and a hypercholesteremia of 1250 mg. per 100 cc. Wille-Baumkauff described them in 2 patients, 1 of which died of common duct obstruction, the other, at the age of 72, of generalized arteriosclerosis and renal arteriolosclerosis.

In all 3 cases, hypercholesteremia was present or highly probable. The values for total blood cholesterol in the present case were low normal. Both normal and high blood cholesterol have been observed in essential xanthomatosis. This discrepancy is important for the interpretation of the nature of the process which terminates with the accumulation of the various lipoids or lipoid mixtures in certain organs or cell systems. Some authors maintain that there is a primary disturbance of the lipoid metabolism and that the accumulating abnormal products are passively stored, preferably in cells to which they have a special affinity.[18,21] On the other hand, it has been claimed that the lipoidoses are diseases of the reticulo-endothelial system and that the accumulation of the lipoid substances is secondary;[24,29] also that lipoid storage may be secondary to protein disturbance of renal disease. Between these points of view, various different interpretations have been brought forth: abnormal ratio between total and free cholesterol,[22] deficiency of lipolytic enzymes,[26] precipitation due to non-optimal dispersion,[30] intracellular disorder of the reticulum cells but not confined to the reticulo-endothelial system.[27]

Since our knowledge of lipoid metabolism is very incomplete, no general agreement can be expected. The present case may throw some light on a few pertinent questions.

1. There was no evidence of a general disturbance of the lipoid

metabolism. The discoloration of the skin was not that usually seen in xanthomatosis but resembled rather that of Gaucher's disease.

2. No diabetes was present. On the contrary, the blood sugar dropped, during an Exton Rose glucose tolerance test, from a fasting level of 124.2 to 82. We realize that a single curve of this type has but limited significance. However, Buerger[4] has collected a number of cases of xanthomatosis which all had low blood sugar values (down to 40 mg. per 100 cc.). These observations are in contrast to the general opinion that the sugar tolerance in xanthomatosis is usually decreased. Whether the attacks of sweating, weakness and mental disturbance, from which our patient suffered, are to be regarded as hypoglycemic episodes or whether they are epileptiform seizures, we are not able to say. It seems more likely, however, that they represent mild hypoglycemic states. At any rate, there was a disturbance of the carbohydrate metabolism which may be connected with the xanthomatous process.

3. The xanthomatosis apparently was limited to the spleen. The liver seemed normal. The pancreas was not examined at the operation. We wish to emphasize again that the endothelial cells did not participate in the changes. It seems unlikely, then, that the lesion was a general one of the reticulo-endothelial system.

4. The anemia, which was the main clinical symptom, was never very severe. It was normocytic, leukopenic, with no evidence of hemolysis. There was no hemosiderosis. The anemia improved after splenectomy and the blood count has been almost normal over a considerable period of time, except for the now present lymphocytosis —a not infrequent sequel of splenectomy in general. By what mechanism the anemia was produced, we are not able to say. The marked improvement after splenectomy certainly suggests that the pathologic changes in the spleen were responsible, perhaps by disturbing the spleen's regulatory influence on blood formation.

5. The general condition of the child also improved after splenectomy, and has remained good for over 2 years. This is additional evidence that the xanthomatosis of the spleen is here a local disorder rather than an expression of a general metabolic disturbance.

The most satisfactory interpretation of the present case seems to be that a local intracellular disorder, perhaps due to an intracellular disturbance of the lipolytic enzymes, has caused the accumulation of lipoids in the reticulum cells of the spleen. Otherwise, no such improvement as seen in the present case after splenectomy, could be explained. The possibility of an associated xanthomatosis of the pancreas may—in a speculative way—be considered in connection with the increased sugar tolerance of the patient and the probably hypoglycemic attacks.

Summary. A case of primary xanthomatosis of the spleen associated with splenomegaly (due to foam cells) and anemia in a non-diabetic child is described. The results of histologic and quantitative chemical analysis of the spleen are reported and discussed. The lipoids chiefly increased were lecithin, cephalin and total cholesterol, thus ruling out Gaucher's and Niemann-Pick's disease.

It is thought that the process represents a local intracellular disorder, perhaps due to faulty action of the lipolytic enzymes. Splenectomy was beneficial.

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CLINICAL OBSERVATIONS ON THE EFFECT OF 3,3′–METHYLENEBIS (4–HYDROXYCOUMARIN)*

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During the last few years, the clinical use[1,5,6,9] of anticoagulants has greatly increased due in large part to the preparation of a non-

* The dicoumarin used in this study was supplied by Dr. Gordon of the Endo Products Company. Dicumarol is the collective trademark of the Wisconsin Alumni Research Foundation.

toxic heparin and to the excellent clinical and laboratory studies of intravascular thrombosis and embolism.*

Widespread use of heparin in the therapy of these conditions has been limited by great expense and difficulty of administration of the drug; it must be given intravenously either in a continuous infusion or by injections 3 or 4 times daily.†

Studies on the pathogenesis of hemorrhagic sweet clover disease in animals[13,15] have culminated in the recent synthesis[17] of a new anticoagulant. This substance, 3,3′-methylenebis(4-hydroxycoumarin), has practical advantages over heparin: it can be given orally and is relatively inexpensive. Its effectiveness and toxicity have not as yet been adequately studied. The object of this presentation is to determine the ability of this drug to act as an anticoagulant in humans and to ascertain its effectiveness and toxicity. An attempt has been made to formulate a satisfactory mode of administration and to assess in general the efficacy of such anticoagulant therapy in clinical practice.

Investigations of the action of 3,3′-methylenebis(4-hydroxycoumarin) in laboratory animals[2,4,13,15] have shown a prolongation of the clotting time and a reduction in prothrombin activity of the blood. Large or repeated toxic doses have been shown to produce widespread hemorrhage and in some animals death. Studies in humans[2,3,8,11,18] have been recorded in relatively few cases; not enough data is available to determine accurately the feasibility of administering this substance in clinical practice. We have therefore given this drug in repeated doses to a group of 71 adult patients.

Materials and Methods. The coagulation time was determined by a minor modification of the Lee and White two-tube method,[7] the average clotting time of the tubes being taken as the coagulation time. Normally, this varies from 8 to 14 minutes.

Prothrombin activity was measured by a modified Quick[10,12] technique using acetone-treated rabbit brain as the source of thromboplastin, 0.1 M sodium oxalate as the anticoagulant and 0.0125 M calcium chloride. The activity was expressed as a prothrombin index by the formula:

$$\text{Prothrombin index } \% = \frac{\text{Control plasma time (seconds)} \times 100}{\text{Pathologic plasma time (seconds)}}$$

The tests were performed on several dilutions (0.85% sodium chloride solution) of plasma, ranging from 62.5% to 25%. At these dilutions, significant changes in prothrombin activity are more readily detected than when undiluted plasma is tested. Normal control plasma was tested at the same time in the same dilutions.

Blood was drawn with minimal stasis in a syringe rinsed with 0.85%

* This includes any intravascular thrombosis or embolism such as bland or septic venous thrombosis, phlebitis migrans, thromboangiitis obliterans, arterial thrombosis or embolism in any organ.

† Since this manuscript was submitted a paper, "A New Practical Method for the Subcutaneous Administration of Heparin," was read by Leo Loewe and Philip Rosenblatt at the Clinical Research Meeting of the New York Academy of Medicine on May 27, 1943. They described a satisfactory technique for the use of heparin by the subcutaneous route. (This article will appear in a subsequent issue of this Journal.—EDITOR.)

sodium chloride solution. All glassware was washed with green soap and dichromate cleaning solution and thoroughly rinsed and dried. Scrupulously clean glassware must be used if reproducible results are to be obtained.

Of the 71 cases, 24 were females and 47 were males. The ages ranged from 20 to 70 years with half of the cases in the 50 to 60 year age group. The patients' weights varied from 100 to 200 pounds. The first 22 patients were selected only in so far as they could remain in the hospital for 2 weeks after the studies were started. They had a variety of diseases: 9 with arteriosclerotic heart disease; 3 chronic liver disease; 3, polycythemia vera; 2, generalized eczema; and the remaining 5 cases with varied clinical conditions. In the other 49 cases, there existed a clear-cut clinical indication for the use of an anticoagulant. In this group are included 17 cases of pulmonary embolism and infarction, 9 cases of thrombophlebitis, 10 cases of peripheral arterial disease of varied etiology, 1 case of thrombosis of the central vein of the retina and 12 cases of embolus or thrombosis in a major artery.

Procedure. The 3,3′-methylenebis(4-hydroxycoumarin) was weighed out in gelatin capsules and was given orally on the average of 8 times to each patient. The doses varied from 200 to 500 mg. and the interval between doses varied from 1 to 7 days. The drug was administered on the first day the patient was studied. Because of the latent period of the action of the drug, which varies from 24 to 72 hours, at least two control readings of coagulation time and prothrombin index could be obtained in all cases. Blood was drawn for study at daily intervals whenever possible. In all, about 900 determinations were done, averaging 13 determinations per patient. The 10 cases of peripheral vascular disease were studied from 1 to 16 weeks. Most of the other cases were studied from 1 to 3 weeks. In these studies we have considered a satisfactory response to the dicoumarin to be an increase in the clotting time of the whole blood to between 15 and 20 minutes and a fall in the prothrombin index of the plasma to between 30% and 50%. At the same time there must not be untoward toxic effect, *i. e.*, hemorrhagic manifestations.

Results. At first, the drug was used cautiously because of the toxicity in animals[2,4,13] and minor toxic effects reported in humans.[12] It soon became apparent however that single doses of 200 to 400 mg. could be tolerated. In general, the plan of dosage was directly dependent upon the individual response of the prothrombin index. The drug was given if necessary in daily doses of 200 to 500 mg. The drug was given in some cases when the prothrombin index was as low as 40%. Our more recent experience, however, is such that dicoumarin is not administered whenever the prothrombin index is less than 50%.

The results of 6 selected cases illustrating variation in response to the drug are shown in Figure 1. A single dose of 400 mg. is usually effective in producing the desired response.[18] Two similar cases, each of which received 500 mg. of the drug showed a marked difference in response: 1 showed a reduction in prothrombin activity and considerable prolongation of the coagulation time over a period of 1 week while in the other case the response was minimal.

Two other cases, essentially similar in age and weight, received approximately 2000 mg. of the dicoumarin in divided doses over an

18 day period. In 1 case the effect was marked and prolonged with evidence of toxicity. The prothrombin index fell to 10% of the normal and the coagulation time rose to 35 minutes. The effect persisted for 7 days after the drug was stopped. In the other, however, the effect was minimal and in no way comparable. The minimal prothrombin index in this instance was 40% while the maximal coagulation time was 20 minutes. Most of the determinations in this case were close to the normal range.

Toxic Effects. In 2 cases transient cramp-like abdominal pains and mild diarrhea occurred a few hours after ingestion of the drug. One of these patients complained of temporary crampy abdominal pains after each ingestion of the drug. Toxic manifestations of bleeding occurred in 8 cases, summarized in Table 1.

TABLE 1.—CASES SHOWING HEMORRHAGIC MANIFESTATIONS

Diagnosis	Dosage of dicoumarin	Prothrombin index at time of bleeding (%)	Site of bleeding and duration	Therapy to combat bleeding	Outcome
Eczema	1200 mg. in 12 days	21	Skin 7 days	None	Skin improved temporarily
Arteriosclerotic heart disease; renal calculus	2000 mg. in 18 days	13	Kidney 2 days	None	Recovery
Generalized arteriosclerosis	2400 mg. in 13 days	13	Kidney 7 days	3 blood transfusions	Fresh blood transfusions did not stop bleeding; recovery
Embolus to femoral artery	1000 mg. in 4 days	7	Amputation stump; rectum 11 days	5 blood transfusions	Death from hemorrhage
Pulmonary infarction; thrombophlebitis	2200 mg. in 13 days	10	Operative incision	5 blood transfusions	Fresh blood transfusions did not stop bleeding; recovery
Arterial embolus	1200 mg. in 7 days	20	Operative wound 5 days	2 blood transfusions	Fresh blood transfusions did not stop bleeding; recovery
Thromboangiitis obliterans	6000 mg. in 12 weeks	6	Gums 2 days	None	Recovery
Pulmonary infarction; thrombophlebitis	1800 mg. in 20 days	20	Lung 1 day	None	Recovery

Liver function tests such as the cephalin flocculation test, hippuric acid excretion test, bromsulphalein test, icterus index, and galactose tolerance test were performed in cases showing toxic effects. No interference with liver function could be demonstrated. Vitamin K had no effect on the circulating prothrombin or on the bleeding tendency. This parallels the experience of Bingham, Meyer and Pohle.[2]

Discussion. Our results show that oral administration of repeated doses of 3,3′–methylenebis(4-hydroxycoumarin) is effective in producing a variable and often marked prolongation of the coagulation time and a reduction in the prothrombin index. The mechanism of this action in decreasing the coagulability of the blood has been thought to be due to this reduction in the prothrombin activity.

In some of our cases, a marked reduction in prothrombin content of the plasma to 10% was not associated with an increase in the coagulation time. This corresponds to our findings in cases of obstruc-

tive jaundice not receiving the dicoumarin, in which a normal coagulation of the whole blood existed with low prothrombin content of the plasma. In many of the other cases receiving dicoumarin, however, elevations of the coagulation time to over 30 minutes were observed when the prothrombin activity fell to low levels (below 30%).

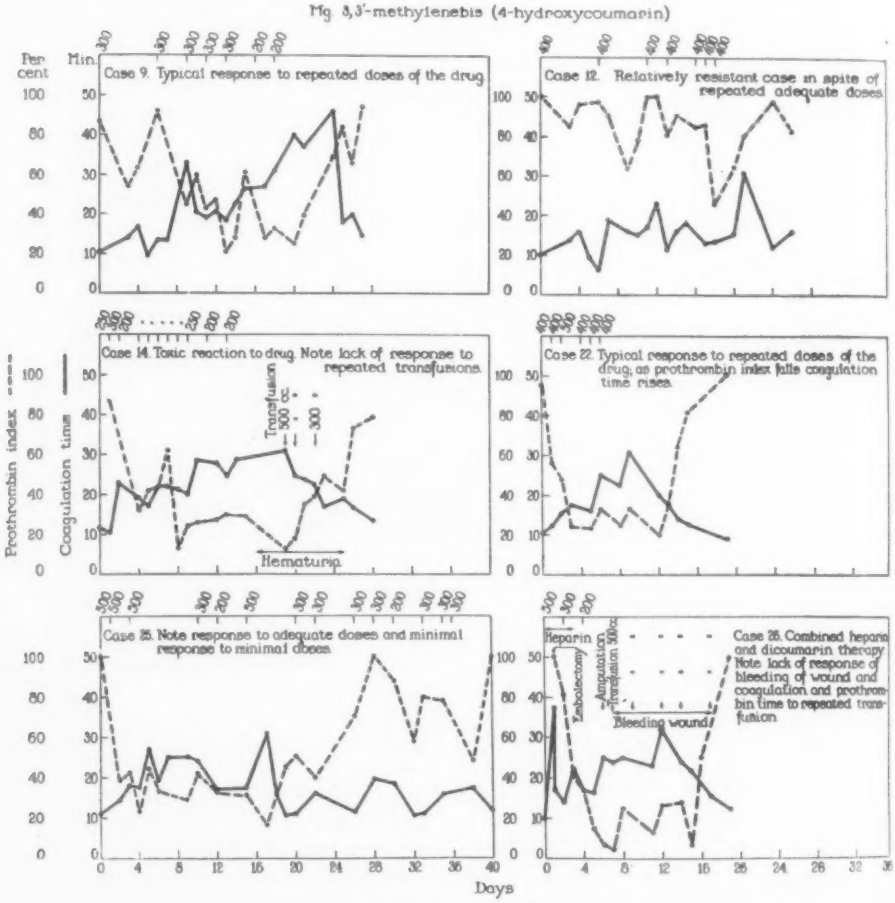
Mg. 3,3'-methylenebis (4-hydroxycoumarin)
Per cent
Min.
Case 9. Typical response to repeated doses of the drug
Case 12. Relatively resistant case an spite of repeated adequate doses
Case 14. Toxic reaction to drug. Note lack of response to repeated transfusions
Transfusion cc. 500 300
Hematuria
Case 22. Typical response to repeated doses of the drug, as prothrombin index falls coagulation time rises.
Prothrombin index
Coagulation time
Case 25. Note response to adequate doses and minimal response to minimal doses
Heparin
Embolectomy
Amputation
Transfusion 500cc.
Bleeding wound
Case 26. Combined heparin and dicoumarin therapy. Note lack of response of bleeding of wound and coagulation and prothrombin time to repeated transfusion
Days

FIG. 1.—Variations in response to mg. 3,3′- methylenebis(4-hydroxycoumarin)

All investigators are agreed that the coagulation defect occasionally seen in obstructive jaundice is a manifestation of an inadequate prothrombin content of the blood. The variable effect of dicoumarin upon coagulation and the differences which often exist between the coagulation defect after administration of this drug and in obstructive jaundice suggest the possibility that dicoumarin prolongs coagulation not only through a reduction in the prothrombin, but through other as yet undetermined effects. Though parenteral administration of vitamin K will restore the prothrombin to normal level in obstructive jaundice.

it has no effect upon the reduced prothrombin brought about by dicoumarin.

It is well established that prothrombin is formed in the liver and that the blood prothrombin falls when widespread liver disease is present or when the supply of vitamin K or its precursors is reduced. The fact that the lowered blood prothrombin following dicoumarin is not elevated by parenteral administration of vitamin K indicates that this vitamin is not directly implicated in the prothrombin deficiency. The remaining assumption, therefore, has been tentatively held, namely, that dicoumarin interferes with the elaboration by the liver of normal prothrombin. It should be emphasized, however, that there is no collateral evidence by various function tests that the dicoumarin affects liver function.*

Our experiences with this drug have led us to employ it in clinical states in which a disturbed coagulability of the blood might be of value. Because of the previously described latent period after the oral administration of the dicoumarin, we and others[11] have given heparin by the continuous intravenous route until the dicoumarin effect became evident. At this time a marked fall in prothrombin activity occurred. Heparin was then discontinued and repeated doses of the dicoumarin were prescribed in a manner similar to the illustrative cases of this communication. At the present writing we have used these drugs in combination in intra-arterial surgery, thrombosis or embolism of a large artery, pulmonary embolism, thrombophlebitis (septic and bland), thrombosis of the central vein of the retina, cavernous sinus thrombosis, thromboangiitis obliterans, phlebitis migrans and subacute bacterial endocarditis.

Our clinical experiences with 3,3′-methylenebis(4-hydroxycoumarin) have led us to certain preliminary conclusions. The individual variation of different patients is so great that a workable dosage schedule for administration cannot be definitely formulated. Many of the patients in whom prolongation of the coagulation time of the blood might prove desirable are acutely ill. If the action of the drug is to be effective, it should be capable of lowering the prothrombin content of the blood fairly rapidly. Trials with different doses are not feasible in such cases. This applies to the clinical situations in which pulmonary embolism, arterial embolism or thrombosis, arteriotomies and certain venous thrombotic states are implicated. The variability of effect of dicoumarin and the inability to predict its action greatly lower its possible usefulness in such conditions.

Similarly, we have occasionally produced an initial fall in prothrombin activity to about 40% of normal but have been unable to maintain this level during the entire period. Despite daily determinations of the prothrombin level of the blood and the fitting of each dose of the dicoumarin to the preceding prothrombin determination, we have not always been able to maintain the lowered levels evenly.

* Since this manuscript was submitted for publication S. Shapiro, M. H. Redish and H. A. Campbell (Proc. Soc. Exp. Biol. and Med., **52**, 12, 1943) have shown that vitamin K in large doses may correct the prothrombin deficiency resulting from minimal effective doses of dicoumarin in humans.

Several instances in which vascular thrombosis occurred during the course of dicoumarin administration may have been due to such temporary escapes during which time the prothrombin levels rose to normal values for 1 or 2 days. This sequence occurred in 1 case of postoperative pulmonary embolism in which massive thrombophlebitis in a lower extremity appeared about 1 week after dicoumarin administration was started. In other cases, however, thrombosis or embolism developed while the prothrombin activity was below 50%. Recurrence of venous extremity thrombosis was seen in 1 case of phlebitis migrans and embolic closure of the iliac artery occurred in a patient recovering from a recent myocardial infarction when the prothrombin content was 25% of normal. Another patient died suddenly probably from pulmonary embolism when the prothrombin was 20%. These observations have led us to question the theoretical grounds upon which anticoagulants are used.

We have observed postoperative bleeding in many cases when dicoumarin was administered either before operation or shortly thereafter. We have also noted a tendency to hemorrhage in any patient receiving dicoumarin in whom an unrelated lesion that might bleed was present. Examples of this include bleeding into the skin in a case of eczema, bleeding from the kidney in a patient with a renal calculus, bleeding from ulcers of the extremities in thromboangiitis obliterans, and bleeding into the pleural cavity following pneumothorax in a case of pulmonary tuberculosis. In regard to operative procedures, hemorrhage at the time of operation may occur only in patients who received the dicoumarin several days previously. If the drug is given on the day of operation, there is no such risk. However, in such cases secondary hemorrhage may occur early in the postoperative course when sutures, drains, or packings are disturbed. Bleeding in all these instances occurred when the prothrombin was less than 20% of the normal.

The 10 cases of occlusive peripheral arterial disease were carefully studied for 3 months. During this period the patients were ambulatory and were examined every other day. Dicoumarin was administered whenever the prothrombin level rose above 60%. Except for slight improvement in an ischemic ulcer of the foot, no beneficial effect of the drug could be observed. There was no essential change in the degree of intermittent claudication or coldness of the extremities in any of these cases during this period.

It should be stated, however, that the toxic effects previously described do not give a true picture of the degree, frequency and severity of toxicity that one should expect from clinical use. Thus the bleeding in 3 cases can be ascribed to over-zealous forcing of the drug in an effort to determine how much could be given. Although the desired effect on the coagulation time and prothrombin index had been produced earlier, drug administration was nevertheless continued.

The prothrombin and coagulation level at which bleeding is likely to occur seems to be between 20% and 5% for the former and over 25 minutes for the latter. The threshold for hemorrhage seems to be more closely related to the prothrombin content than to the coagula-

tion time. The hemorrhagic tendency, once developed, is likely to persist until the prothrombin index rises to 30% or more and the coagulation time falls below 20 minutes.

Four cases received repeated transfusions of fresh blood in an effort to elevate the circulating prothrombin and diminish the bleeding tendency. In none of these instances were dramatic effects observed, and we believe that bleeding ceased only after the dicoumarin effect had worn off and the prothrombin level had become elevated. In these cases it was apparent that transfusions served only to maintain the hemoglobin level and had but little effect on the cessation of bleeding. There was one death from hemorrhage despite 5 blood transfusions.

Our experiences with the effect of dicoumarin in promoting the healing of ulcers of the extremities due to arterial insufficiency are restricted. In 1 case of arteriosclerotic occlusive peripheral vascular disease with diabetes mellitus, slow healing of a large ulcer occurred over a 3 month period. During this time the plasma prothrombin was maintained between approximately 30% to 50%. Occasional oozing of blood from the ulcer occurred. At the termination of treatment, the ulcer was one-half its previous size and its base was granulating well. In another case, rapid healing of a refractory arteriosclerotic ulcer occurred within 2 weeks.

Plan of Therapy. The following therapeutic plan for prolongation of blood coagulation with 3,3′-methylenebis(4-hydroxycoumarin) may be found useful in certain instances. It is our present procedure to administer orally as the first dose 300 mg. to a patient weighing 130 pounds or less, or 400 mg. to one weighing over 160 pounds. On the second day, an additional 200 mg. is sometimes given. The subsequent doses will depend upon the results of the coagulation and prothrombin tests. It is imperative that prothrombin tests be performed daily. If no effect is observed by the third day, a dose of 300 mg. may be given. If a marked effect is observed, however, further administrations of the drug are withheld. Repeated doses, as much as 300 mg. or more daily, may be required in resistant cases. In other instances smaller doses at less frequent intervals are all that is required. Such a general scheme, in which dosage is controlled by tests performed at daily intervals, will enable one to exercise control.

Conclusions. 1. The oral administration of 3,3′-methylenebis(4-hydroxycoumarin) produces a marked fall (after a 24 to 72 hour latent period) in the prothrombin content and prolongation of the coagulation time of the blood in most cases.

2. There is great variability in the degree of response to this drug. A definite fixed dosage schedule cannot be made. Patients must be individualized.

3. Because of the variable response and latent period the drug has not always been useful in the therapy of arterial thrombosis or embolism, arteriotomy or major pulmonary embolism.

4. Because of the danger of hemorrhage, the drug has not proved useful during or shortly after operative procedures or in patients with unrelated lesions from which bleeding might occur.

5. Transfusions of fresh blood do not arrest the hemorrhagic tendency due to dicoumarin.

6. Several instances have been observed in which embolism, thrombosis or progression of existing venous thrombosis have occurred despite a low blood prothrombin induced by dicoumarin.

7. Symptomatic improvement in the 10 cases of occlusive peripheral vascular disease was not observed during a 3 month period while the prothrombin remained depressed as a result of dicoumarin administration.

8. It is possible that dicoumarin affects blood coagulation not only by lowering the prothrombin content, but through other mechanisms.

9. We believe that further trial of the drug is required before its effects in peripheral venous thrombosis and in pulmonary infarction can be determined.

10. dicoumarin should not be administered if the prothrombin index is less than 50%.

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HEMATOPORPHYRINURIC NEURITIS

Report of a Case

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Of all the unusual conditions involving the nervous system which produce a neuritis, excluding those due to the heavy metals, vitamin deficiency, trauma or infection, there is none about which as little is known as hematoporphyrinuric neuritis. In this condition the neuritis

tends to be motor in nature, usually affecting the upper extremities, but often beginning in the lower extremities and ascending progressively to produce a clinical picture similar to Landry's paralysis. In many cases, the paralysis ascends to the medulla. This is followed by death from respiratory failure. Pathologically, the nerve involvement is not specific and in most cases reveals only the usual degenerative changes in the myelin sheaths and axons with degeneration or loss of anterior horn cells. Clinically, neuritis caused from hematoporphyria can be recognized because of its association with acute gastric symptoms such as colic and pains radiating into the loins. However, it must not be confused with lead colic, which is also often associated with neuritis. Unfortunately, little is known either about the cause of hematoporphyria or about the manner in which it affects the nerves.

Since the disease is often initiated by repeated acute colicky pain in the abdomen, it may first come to the attention of the surgeon or internist. However, the red or wine-colored urine may send the patient to the urologist, or the sensitivity of the skin to light and the formation of bullæ after exposure to sunlight[3] may bring the dermatologist into the picture. Muscular weakness and paralysis with occasional mental symptoms may involve the neuropsychiatrist before the condition is diagnosed. It is, therefore, a disease of general interest to every medical man. Because the disease is not well understood, study of individual cases should be of considerable value in furthering our knowledge of the meabtolism of pigments in the human body.

Case Report. F. U., a white male, aged 47, was first seen in consultation with Dr. Royal T. Liles at Touro Infirmary on August 11, 1942, in a semiconscious, moderately delirious condition, occasionally groaning with pain and apparently dehydrated. Muscular weakness of the extensors of the wrists and feet was obvious. He was apparently unable or unwilling to use his arms even when restlessly tossing about.

The patient had been nervous since he had had generalized abdominal pains in 1932 when a papilloma was removed from the bladder by transurethral fulguration. In 1940, he had such an acute attack of abdominal colic and discomfort that a laparotomy was done, but nothing was found except some adhesions. No information was obtainable as to whether the urine was discolored or whether there was any muscular weakness on that occasion, but shortly after the operation there appeared a transient paralysis of the left arm which lasted about 5 days. The abdominal symptoms were not relieved, and the patient continued to complain intermittently of colicky pains. Recently, this had become so acute that he was brought to the hospital. For several days prior to his admission he had been vomiting, especially after eating. Bowel movements remained regular until 2 days after admission when he began to have diarrhea, averaging 10 to 20 stools daily. These were unformed, moderately light-colored, and watery. The patient continued to have severe abdominal pains with delirium and progressive weakness of the extremities. Urinary retention developed, necessitating the insertion of an indwelling catheter into the bladder.

The patient had had the usual childhood diseases, and had had gonorrhea 10 years previously. He imbibed alcoholic beverages excessively, consuming approximately 1 pint a day for several years.

The family history was significant. A sister had died of an undiagnosed condition with abdominal colic and progressive neuritis at the age of 22. A brother had had a severe illness characterized by abdominal colic and weakness from which he had gradually recovered.

Examination of the patient upon admission revealed a blood pressure of 214/110, pulse 120 and temperature 99.4° F. The patient was lying on his back, apparently semiconscious, groaning faintly, restless and unable to coöperate with the examiner. All of the cranial nerves appeared normal except for the fundi, which showed moderate sclerosis of the vessels. The teeth were not discolored. The tongue was shining and purplish red in color. Motor weakness of both upper and lower extremities was obvious and wrist drop was apparent. Sensation could not be tested satisfactorily. There were no other abnormal physical findings except for an old healed right rectal incision. There were no masses in the abdomen, and tenderness in this region could not be elicited.

Roentgenograms of the chest on August 11, 1942, were negative. A gastro-intestinal series showed hyperperistalsis with distention of both small and large bowel loops.

On admission, July 30, 1942, the red blood cell count was 5,100,000 with 80% hemoglobin and the white blood cell count was 7900 with 71% polymorphonuclear cells. Urinalysis was negative. On July 31, 1942, the non-protein nitrogen was 42.9 and dextrose 100. Wassermann reaction was negative. On August 7, 1942, the white blood cell count had increased to 12,500 with 75% polymorphonuclear cells. The urine showed hyaline casts. Stools were negative for parasites and ova. On August 11, 1942, the urine was wine-colored and showed a positive urobilinogen of 1:258 and a positive test for uroporphyrin, Type 1. On August 12, 1942, the non-protein nitrogen had risen to 66. Plasma sodium chloride was 482 and carbon dioxide combining power 33.4. All febrile agglutinations were negative. Blood cultures were negative.

From the day of admission on July 30, 1942, abdominal colic was constant. On August 7, the patient had 25 bowel movements with much tenesmus. The temperature was 101° F. On August 9, diarrhea was still present, but the temperature had gone down. On this day extreme weakness of the left arm and both legs was evident. On August 11, urinary retention developed and the patient was catheterized. A dark red wine-colored urine was obtained. On August 12, 1942, the patient began to show bulbar symptoms, having obvious difficulty in coughing and swallowing. He was placed in an oxygen tent. On August 13, 1942, he became cyanotic, and there was evidence of respiratory paralysis. He was placed in a respirator, but expired the same day.

Findings at Autopsy. A complete autopsy was performed on August 14, 1942, but only the pathologic findings which were asso-

ciated with the condition which contributed directly to the patient's death will be discussed.

Gross Pathology of the Brain and Spinal Cord. No evidence of thrombosis was noted in the superior sagittal sinus. The dura stripped with ease from the pia arachnoid and no subdural hemorrhages were noted. The pia arachnoid was grayish white in appearance and in scattered areas over the cerebral hemispheres showed areas of thickening which varied in size from 1 to 5 cm. in diameter. The brain was removed and sectioned. No flattening of the cerebral gyri was noted. Serial sections made through the cerebral hemisphere showed no evidence of gross pathologic changes. No changes were noted in the cerebellum except for some gelatinous degeneration of the dentate nucleus. The spinal cord was removed by the anterior approach and serial sections through this showed no evidence of gross pathologic changes. The leptomeninges over the sulci of the frontal and parietal lobes were thickened and fibrosed. There were worm-like areas of depressed and narrowed convolutions of the cortex over the frontal and parietal lobes bilaterally. A slight degree of arteriosclerosis of the basal vessels of the brain was present.

The pathologist reported the following anatomic diagnoses: cardiac hypertrophy; pulmonary atelectasis; acute ulcerative colitis; benign nephrosclerosis; chronic peritonitis; focal cortical atrophy; leptomeningeal fibrosis; and cerebral arteriosclerosis (mild).

Spectroscopic examination of the urine revealed the presence of uroporphyrin, Type 1.

Microscopic Findings of Brain. The leptomeninges were greatly thickened and contained large numbers of fibroblasts. Many of these were filled with a yellow pigment. There were also numerous macrophages present in this tissue and some of these were also filled with the same pigment. A few free red cells were seen in the subarachnoid space over the medulla. There was a patchy loss of ganglion cells in the cortex. Many of the remaining cells were edematous. The ependymal lining was intact, but there was a patchy subependymal gliosis. In the white matter there were patches of glial scarring and many *Corpora amylocea.* There was a pronounced Monckeberg's sclerosis of the internal capsule and basal ganglia. The arterioles of the subarachnoid space over the cerebellum showed considerable hyalinization.

Additional microscopic diagnoses included myocardial scars, acute cholangitis, fibrosis of leptomeninges, focal cerebral atrophy, Monckeberg's sclerosis of cerebrum and arteriolar hyalinization, subarachnoid space.

Pathologist's Comment. This is fundamentally a case of hematoporphyrinuria, the cause of which is not known. There was no history of having taken any of the drugs such as trional or veronal which, it is believed, may predispose to this condition. As is usual in these cases, no significant visceral lesions were found. It is quite probable that the lesions in the colon were of a terminal nature and were associated with the uremia. It does not seem likely that the mucosal

lesions were present at the time of the roentgenographic examination inasmuch as they were all of a very recent nature. However, the colon could have been distorted because of adhesions.

Comment. Hematoporphyria is rarely seen in man. By 1940 less than 200 cases had been reported in the literature. The condition affects women more often than men and the initial attack usually occurs in the fourth or fifth decade. There may or may not be a familial history. The disease appears to be a metabolic disturbance intimately connected with hemoglobin synthesis and degradation, and is usually associated with the excessive excretion of porphyrin by the urine (porphyrinuria). Porphyrinuria is often so great that the abnormal wine color of the urine leads to its diagnosis.

First recognized by Gunther in 1911, this disease was later classified by him into three types: (1) congenital hematoporphyria;[5] (2) acute idiopathic hematoporphyria;[3] and (3) acute toxic hematoporphyria (due to lead, veronal, sulfonal and other barbiturates).[2] Up to 1940 less than 30 cases of the first type had been reported, 46 of the second type and about 100 of the third. In health, the urine, feces and bile contain traces of a porphyrin, but in porphyrinuria there is an abnormal excretion of this substance in the urine. The feces may contain porphyrin (coproporphyrin) and the intestine may also be the site of degradation products of hemoglobin, protoporphyrin and deuteroporphyrin. These are all related pigment substances.

Hematoporphyria is characterized by a fairly acute onset of severe, cramplike, abdominal pain which may radiate down to the thighs and flanks or even up to the chest. Nervousness, exhaustion, emotional instability or insomnia may precede the initial attack by weeks or even months. Nausea and vomiting may be associated with the abdominal pain. Although these patients usually do complain of constipation, this is not necessarily true. Convulsions and states of delirium may develop during the attack. There may be weakness of the extremities of a motor type which may ascend to involve the medulla, and this may be associated with dysphagia and respiratory paralysis. As a general rule, as the symptoms rapidly increase in severity, the visceral pains and distention often lead to a mistaken diagnosis and subsequent laparotomy. An increase in pulse rate, mild fever, moderate leukocytosis, urinary retention, toxic delirium, excitement or hallucinations may confuse the picture. The patient may complain of continued pains and paresthesias in the extremities, associated with weakness of the distal extensors. Reduced or absent tendon jerks may disclose a progressive multiple neuritis. The proximal or peripheral muscle groups may be affected, and objective sensory changes may or may not be found. Of particular interest are those cases that show an acute ascending form of paralysis which finally produces bulbar paralysis usually with a fatal outcome.[1] Approximately 50% of patients succumb to the first acute attack.

Roentgenograms usually reveal dilatation of some part of the intestinal tract, often of the large bowel. The urine is characteristically brownish-red or burgundy wine in color and contains large amounts

of porphyrin recognized by spectroscopic examination. Spinal fluid has been found normal in several cases, though pathologically it is not characteristic.

Acute degenerative lesions may be found in the peripheral nerves and in the spinal cord. The ventral horns may show swelling, eccentric nuclei or complete disappearance. The nerves and spinal roots may show disintegrated axons and myelin sheath degeneration. In general, the pathologic changes are of a parenchymatous toxidegenerative type.

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CARBON DIOXIDE BY INHALATION AS AN EXPECTORANT

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In 1905 Haldane and Priestly[12] first demonstrated that the carbon dioxide of the blood normally controls respiration. Shortly thereafter Henderson[14] expounded the rôle of carbon dioxide as a respiratory stimulant. In a large series of subsequent publications Henderson[15] advocated the therapeutic application of carbon dioxide by inhalation after anesthesia and surgical operations, in the treatment of carbon monoxide poisoning, whooping cough, asphyxia of the newborn, resuscitation from drowning, severe electric shock, morphine poisoning, and failure of the respiration from various other causes. Henderson recommended the inhalation of carbon dioxide for the purpose of controlling the respiration during anesthesia and for the prevention of the depression of the respiratory center in deep anesthesia. He attributed the development of postoperative atelectasis to the lowered tonus of the respiratory muscles of the thorax, particularly the diaphragm, caused by the anesthesia and by the postoperative depression of vitality. The diminished tonus of the respiratory muscles leads to an incomplete expansion of the thoracic cavity during inspiration. Thus the lungs are underinflated and bronchi or bronchioles become easily obstructed by accumulated mucus. Subsequent to such occlusion the air is gradually absorbed from the occluded area that, consequently, becomes atelectatic. This area represents a predilectional place for the development of postoperative pneumonia. Inhalation of carbon dioxide is capable of producing an increased tonus in the respiratory muscles and

thus of reëstablishing the normal inflation of the lungs; consequently it acts as a powerful preventative against postoperative atelectasis and pneumonia. Excellent results were noted by MacKenzie[20] with the use of carbon dioxide for deëtherization and for the prevention and treatment of postoperative atelectasis and pneumonia in 5000 cases. Scott and Cutler[24] recommended the inhalation of carbon dioxide in all patients operated on under general anesthesia and advised the administration of 30% carbon dioxide and 70% oxygen in addition to the air breathed for periods of about 1 minute at a time, interspersed with rest periods of about 2 minutes, at the end of the operation. Henderson and Haggard[16] attributed the beneficial effect of carbon dioxide inhalation in carbon monoxide poisoning to the stimulation of the respiratory center that is followed by vigorous respirations which serve the rapid elimination of the carbon monoxide from the system. Its use for resuscitation of the newborn was recommended on the basis that carbon dioxide is quite as effective a stimulant of the respiration in the non-breathing or poorly breathing infant as it is in carbon monoxide poisoning. Similarly intense depression of the neuro-respiratory system in morphine poisoning can be counteracted effectively by the stimulating effect of carbon dioxide. Hunter and Mudd[18] and Robinson and Selesnick[23] found that patients with alcoholic coma can be rapidly revived. Also Henderson[15] suggested carbon dioxide inhalations for the treatment of cyanide poisoning, particularly if the poison has been absorbed through the lungs. Hurst[19] and Campbell and Poulton[7] reported favorable results from carbon dioxide inhalations in bronchial asthma. Churchill[9] used the Henderson inhaler for the administration of carbon dioxide for aiding the reëxpansion of the lung in patients who were operated on for empyema. He found that this method was superior to blowing or breathing exercise. Striking results were observed by this procedure by Alison[1] in the treatment of acute bronchitis. He administered a mixture of carbon dioxide and oxygen in a tent for 15 minutes every hour.

The various physiologic responses to the inhalation of carbon dioxide have been extensively studied. Prinzmetal[22] found that the inhalation of 10% carbon dioxide in dogs rendered the intrapleural pressure more negative: from −4.5 to −8, and simultaneously increased the inspiratory chest circumference. By the inhalations of concentrations higher than 10% the intrapleural pressure not only becomes more negative on inspiration but also much more positive on expiration. Grueneberg and Viethen[11] recorded their observations in children from 3 weeks to 14 years of age: the effect of the inhalation of 1% carbon dioxide began in 6 minutes and consisted of an increase in the respiratory volume by 33 to 50%; 2% carbon dioxide began to act in the third minute, and 3% carbon dioxide in the second minute; by the inhalation of 4% carbon dioxide not only the respiratory volume was increased to 100% but also the respiratory rate. Concentrations of carbon dioxide from 5 to 10% increased the respiratory volume to 150 to 400%. They noted that the respirations returned to the pretreatment rate and volume in 2 minutes after the inhalations were discontinued, and

also that if higher concentrations were given with brief intermissions the respiratory center became more sensitive to lower concentrations of carbon dioxide. Similar observations were made by Hitzenberger.[17] The observations of Heller and his associates[13] are of significance from the standpoint of the practical application of this method of treatment. They used 5 and 7% carbon dioxide in air and found that in young healthy adults the respiratory minute volume was increased from 10 to 15 liters to 40 liters by 5% carbon dioxide and to 62 liters by 7% carbon dioxide. The response was variable in different subjects: although the respiratory stimulation was usually vigorous, there were some persons who showed only slight response in minute volume increase to 5 and even to 7% carbon dioxide. Also, there was a fair amount of variation in the same person on different days. Brown[5] observed that in healthy man the maximum stimulation of the respiratory center can be attained by the inhalation of 10.4% carbon dioxide.

Inhalation of carbon dioxide affects the bronchial tract directly and indirectly. Passive motion of the bronchial branches was observed by Macklin[21] following the instillation of iodized oil. Gordonoff[10] studied kymograms of the bronchographed lung. He found that the motion of the bronchi is synchronous with that of the ribs and the diaphragm. Castex and his associates[8] recently described active movements of the bronchi during consecutive phases of the respiratory cycle that were visualized with the aid of bronchocinematography. These active movements consist of changes in the length and caliber of the bronchi, peristalsis, undulation and torsion. The normal bronchi are elongated and dilated during inspiration and shortened and narrowed during expiration. Brunn and Brill[6] and Brown[4] observed the effect of carbon dioxide inhalation upon the bronchial tract during bronchoscopy. They report that the administration of carbon dioxide produced: (1) an increase in the rate and depth of respirations; (2) violent movements in the tracheobronchial tree and alterations in the shape of the lumina of its branches, thereby tending to free adherent mucus; (3) blanching of the mucous membrane of the trachea and bronchi.

We began the clinical use of carbon dioxide inhalations in tuberculous patients in 1930 and reported some of our observations in previous publications.[2] We were prompted by the favorable experience of others in various pulmonary diseases and by the difficulties often encountered in the management of cough in tuberculous patients. There are a great many cases of chronic pulmonary tuberculosis in which the well known expectorants fail to bring relief. The reasons for this are several: (1) the inflammatory exudate accumulating in the bronchial tubes may be too viscid and tenacious; (2) a dense mucopurulent plug may obstruct the way of free drainage from the bronchi; (3) the lung may be in a stage of subventilation. It has been pointed out by several investigators that without adequate inflation of the lung no adequate expectoration is possible: the air compressed by the diaphragm and the chest muscles represents the only agency that

actually expels inflammatory products from the bronchi at the moment when the previously tightly closed epiglottis suddenly opens. Subventilation with its consequent predilection to insufficient cough may be brought about by various factors such as reflex spasm of the thoracic muscles due to pleural pain, general debility, and diminished irritability of the respiratory center to normal stimuli. Furthermore, obstruction of branches of the bronchial tract may prevent the access of air to sections of the lung distal to the point of obstruction, thus rendering impossible the elimination of inflammatory exudate by coughing from this part of the lung. During the course of pulmonary tuberculosis such bronchial obstruction may be caused not only by a thick, viscid, mucopurulent plug, but also by inflammatory edema and swelling of the mucous membrane, bronchospasm, overgrowth of granulation tissue, kinking, deformity or collapse of the bronchus due to ulcer formation or bronchiectasis, and by fibrous bronchostenosis that may become easily occluded by even small amounts of mucus.

The use of opiates is universal for the treatment of cough during the protracted course of pulmonary tuberculosis. Their merit in controlling certain types of cough has been firmly established. Still, one should keep in mind that by their use the normal peristaltic movements of the bronchi and the full action of the ciliary epithelium are decreased or abolished. Such effect of the opiates in case of accumulation of mucopurulent tuberculous exudate in the bronchial tract would actually create a vicious circle by impeding bronchial drainage. To avoid such paradoxical situation it is advisable to use narcotics discriminatingly in the management of cough. Indeed, the rational treatment of cough should be directed against its cause; and if its cause lies in the presence of abnormal amounts of mucopus in the bronchi, the adequate evacuation and cleansing of the bronchial tract should be the primary objective. Only when this is accomplished should one resort to narcotics as adjuncts.

Method. The apparatus used in our work consists of a tank, containing a mixture of 10% carbon dioxide and 90% oxygen, mounted on a small platform on casters that makes it possible to give the inhalations to bed patients. An oxymeter regulates the flow of gas per minute. Originally we used an ordinary mask used for general anesthesia; more recently the B.L.B. mask is being used. The inhaler is connected to the tank by a rubber tubing. A rubber bag which serves as a small reservoir is attached to the inhaler. In some patients it was found expedient to give the inhalations through a glass tube instead of the mask: either because they were reluctant to accept the mask, or the respiratory stimulation was too strong from closed inhalation of the mixture. It is fully realized that, when inhalations are administered through a glass tube held in the patient's mouth, the admixture of air and dilution of carbon dioxide take place; but results by this so-called open method are quite satisfactory. The open method is recommended for patients who are markedly debilitated or who show some of the possible side-effects when the closed inhaler is used. It is a good policy to explain to the patient briefly the mode of action of the inhaled gas, and the expected changes in respiration, and the probable subjective symptoms. Inhalations by the closed method are given by a nurse. After proper instructions, inhalations through a glass tube can be administered without constant supervision; however, it is the responsibility of the nurse to regulate the flow of the gas, and time of the treatment. As a

rule, the meter is set to 4 to 5 liters per minute for closed inhalations and to 5 to 7 liters per minute for the open method. The length of each treatment varies from 5 to 15 minutes; and the inhalations are administered once, twice, or three times a day. It is necessary to observe the patient closely during the first treatment. His respiratory response and subjective reactions determine the conduct of further treatments. Since a self-experiment on one of us (A.L.B.) by the closed method, we fully appreciate the sensation experienced by the patient when marked inspiratory expansions of the chest are induced by carbon dioxide. They are conscious of breathing deeper and subsequent to the treatment they describe their experience in such terms as "the chest feels clear and cool" and "the chest feels so much lighter." If it is noted that the respirations become too strenuous, the inhalations should be given with brief (1 minute) interruptions. In rare instances, when the closed method is used, it may be necessary to reduce the flow to less than 4 liters per minute. Most patients appear quite comfortable, as if in euphoria. The latter can be explained: (1) by the presence of 90% oxygen in the gas mixture that is bound to counteract anoxemia; (2) by loosening up mucopurulent bronchial plugs and obstructive sticky, tenacious inflammatory exudate: the access of air is secured to underinflated regions of the lung; (3) by increased inspiratory expansion of the chest wall and by increased descent of the diaphragm atelectatic areas are stretched out and become aërated. In some of our patients we noted some transient minor side-effects of carbon dioxide inhalations such as hot sensations, palpitation, weakness, frontal headache, and slight dizziness. None of these symptoms interfered with the treatment when proper adjustments were made in the method of administration. In the beginning, the treatments are given daily; subsequently, the frequency of inhalations can be reduced, depending upon the relief obtained. Some patients were obliged to take them daily for an extended period of time, while in others the interval between inhalations could be increased to a week or even to 11 days. Carbon dioxide is an effective therapeutic agent, and in its use utmost individualization is required.

The retention of infected exudate in the bronchial tract harbors serious consequences: (1) the production of atelectasis; (2) the absorption of inflammatory products that may lead to constitutional symptoms; (3) the intracanalicular spread of the disease; (4) by its check-valve action may lead to the development of blocked cavities. It is also obvious that excessive, unproductive cough interferes with the general rest of the patient, and particularly with the rest of the diseased lung; it may handicap the approximation of cavity walls and the closure of cavities, and choking spells, vomiting, headache and insomnia may be its disagreeable consequences. Furthermore, excessive cough may accelerate the development of emphysema, may cause dyspnea, cyanosis, thoracic pain, and spraying of infected material from one part of the lung to the other.

In carbon dioxide by inhalation we have a most efficient expectorant at our disposal. With its aid we are able to change an excessive yet unproductive cough into a useful cough and thereby eliminate dangers inherent to the accumulation, retention, and insufficient expectoration of inflammatory products. According to our experience carbon dioxide liquefies the mucopurulent exudate in the bronchi and reduces its viscosity so that the sputum becomes thinner, more serous and watery; furthermore, the sputum is loosened up and consequently it is expectorated without strain or effort. The prompt relief obtainable by this treatment is best expressed in the comments of patients: "the cough

is not so dry, it is loose," "the cough does not jar me any more," "the cough is less, and not tight as before," "I do not have to exert myself when coughing," "I have no more dry spells of coughing," etc.

We have noted that following inhalations the amount of expectorated sputum is greater than before treatment, and also that adequate evacuation of the bronchi insures for the patient comparatively long periods of rest free of the annoying cough. Incidental by-effects of the satisfactory pulmonary drainage by carbon dioxide are: relief from dyspnea, undisturbed sleep during night, and improvement in the general subjective feeling. Often patients remarked how a feeling of pressure and heaviness was relieved by the treatment, that following inhalations their chest felt freer "like a loose sponge," and how much easier they were able to move about. Also we have noted the disappearance of chest noises and pharyngeal cough irritation.

When satisfactory evacuation of the bronchi has been accomplished, the amount of sputum becomes gradually less, unless further mucopurulent accumulation takes place during the interval between treatments. It can be seen, therefore, that the frequency of inhalations and gas flow per minute have to be individualized and adapted to the changing requirements of the patient. We have found that the inhalation of carbon dioxide not only alleviates distressing cough but also enables one to reduce the consumption of narcotics and expectorant drugs.

The recent painstaking investigations of Basch, Holinger and Poncher[3] concerning the effectiveness of carbon dioxide and of the commonly used expectorants confirm our own clinical findings. They studied the influence of ammonium chloride, potassium iodide, fluid extract of senega, fluid extract of ipecac, and emetine hydrochloride, and compared it with the effect of carbon dioxide. They found that carbon dioxide acts as a real expectorant by diluting the sputum—that is, by lowering its viscosity and reducing its solid contents. They state that in comparing the physical and chemical properties of the sputum after the use of carbon dioxide inhalations with the same properties after the administration of drugs one at once realizes the greater liquefaction of the sputum caused by carbon dioxide: "since in this treatment there is no interference with the chemical properties of the sputum through the secretion of the administered drugs into it, the dried residue, the amount of ash and the total nitrogen content are regularly markedly lowered."

As to the selection of cases for this treatment, it is indicated whenever there is an accumulation and retention of inflammatory exudate in the bronchial tract and its evacuation—in spite of strenuous cough—is inadequate. There are patients that should not be given this treatment: (1) patients with recent pulmonary hemorrhage; (2) those with marked emphysema; (3) when widespread pulmonary fibrosis is present without atelectasis, bronchiectasis or mucopurulent retention in the air-passages; (4) cases of acute plastic pleurisy and pleurisy with effusion; (5) hypertensive patients; and (6) when the cause of cough is outside of the lungs.

Conclusions. From our experience with this method of treatment during the past twelve years we have arrived at the following conclusions:

1. Carbon dioxide by inhalation is a most efficient expectorant.

2. When a mixture of 10% carbon dioxide and 90% oxygen is administered by the closed method, through a B.L.B. mask, or by the open method, through a glass tube, it is tolerated by the patients well. Occasional minor by-effects do not interfere with the treatment.

3. The amount of gas mixture given and the frequency of treatments should be adapted to the individual case.

4. The relief obtained by the inhalations of carbon dioxide is noticed subjectively and objectively: (*a*) spells of strenuous, exhausting coughing are prevented and thereby rest is secured for the patients and particularly for the lungs; (*b*) an unproductive cough is transformed into a useful one; (*c*) directly after inhalation the amount of expectorated sputum is increased and its character changes from a heavy, thick and tenacious type into a thinner, serous and more watery kind; (*d*) the use of expectorant drugs and narcotics can be reduced.

5. The effectiveness of carbon dioxide is attributable mainly to the following factors: (*a*) it is a powerful respiratory stimulant and induces increased inspiratory movements of the thorax that, in turn, cause a stretching and dilatation of the bronchial tubes; (*b*) it stimulates the myo-elastic structures of the lung and leads to a forceful peristaltic movement of the bronchi; (*c*) it liquefies mucopurulent inflammatory exudate that stagnates in the bronchial tract.

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THE MAZZINI SLIDE FLOCCULATION TEST—SENSITIVITY OF ITS ANTIGEN

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The value of a laboratory test often depends on its variability and stability under different conditions. Thus with the Mazzini flocculation test for syphilis as well as with other tests for syphilis, there is a minimum and maximum degree of sensitivity of its antigen according to its age.

When properly prepared and used, this antigen gives reliable results comparable to many of the established, more complicated and more difficult tests which have stood the test of time.

In the 1941 Original Methods Survey of tests for Syphilis conducted by the U. S. Public Health Service,[2] the Mazzini test was found to have a specificity of 99.6 in normal and non-syphilitic bloods and a specificity of 95.8 in all bloods including leprosy and malaria. The sensitivity was found to be 78.6 in all syphilitic bloods, including early, treated and latent cases.

The Mazzini Test.[1] The Mazzini antigen is prepared by the alcohol and ether extraction of beef heart powder and powdered egg yolk. The acetone insoluble lipoids are added, and the antigen is cholesterinized on the basis of a previous titration. To prepare the final suspension, 0.4 cc. of the cholesterinized antigen is added to 3 cc. of normal saline solution buffered at a pH of 6.3 to 6.4. The suspension is shaken for 10 seconds and then allowed to stand at room temperature for 3 to 4 hours at which time it reaches its maximum sensitivity. For emergencies Mazzini recommends that the antigen be ripened in a refrigerator at 6° to 8° C. for 15 minutes.

The suspension is drawn into a 5 cc. syringe fitted with a 25-gauge needle. To 0.05 cc. of serum on a slide, 1 drop of antigen is added from the syringe. The slide is rotated for 4 minutes and the results are read under low-power magnification. Either paraffin or sealing wax rings may be used on the slides.

Mazzini attributes the specificity and increased sensitivity of his test to the use of egg yolk, the lipoid-cholesterin ratio, the serum-antigen ratio, and the concentration of the hydrogen ion in the final suspension.

Experimental Material.—Because this test has shown an increased sensitivity correlated with a high specificity, and since it is a quick and easily performed test, it is adaptable for testing blood donors. In this connection we wished to know whether the antigen should be prepared whenever needed by ripening it in the refrigerator for 15 minutes or whether it would have as great a sensitivity if made once a day and used for 27 to 28 hours, thereby allowing a single preparation of antigen each day.

For this purpose we employed 4 types of antigen suspensions: (1) suspensions which had stood 4 hours at room temperature; (2) suspensions which had been refrigerated 6° to 8° C. for 15 minutes; (3) suspensions which had been refrigerated for 15 minutes at 6° to 8° C. followed by 1 hour at room temperature; and (4) suspensions which had stood from 27 to 28 hours at room temperature. These antigens were tested against unknown sera and known syphilitic sera from patients in various stages of infection.

One series was done during the winter at room temperature of approximately 73° F. and another during the summer with the temperature in the serology laboratory ranging from 80° to 94° F.

Winter Series. When the specificity of the 4 types of antigen suspension was compared, it was found that out of 340 sera negative with the 4 hour antigen only one showed a doubtful reaction, which was with the 27 to 28 hour antigen. This was not of statistical significance.

When the sensitivity of these 4 types of antigen suspensions was compared it was found that 103 sera showed reactions with the 4 hour antigen, 94 reacted with the 27 to 28 hour antigen, 74 reacted with the 15 minute refrigerated antigen, and 85 reacted with the antigen which had been refrigerated for 15 minutes and then allowed to stand 1 hour at room temperature. This is graphically illustrated in Figure 1.

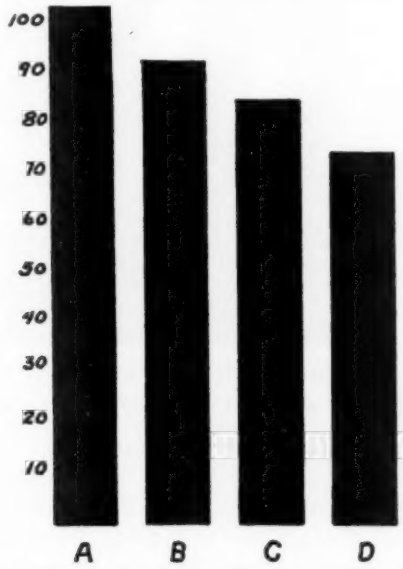

FIG. 1.—Comparison of antigens and number of reactions—winter series. *A*, 4 hour antigen, *B*, 27–28 hour antigen; *C*, antigen refrigerated 15 minutes plus one hour at room temperature; *D*, antigen refrigerated 15 minutes.

The statistical method of analysis was used to determine whether the difference among the results is significant when based upon a sample of this size. The formula for the standard error of the difference between two percentages $\left(\sqrt{\frac{p_1q_1}{n_1}+\frac{p_2q_2}{n_2}}\right)$ * was employed.

* p = % of occurrence; q = % of non-occurrence; n = number in the sample.

When the 27 to 28 hour antigen suspension, which failed to react 9 times (8.7%) was compared with the antigen suspension refrigerated for 15 minutes, which failed to react 29 times (28.9%), the standard error of the difference was 5.39 and the difference was more than 3 times the standard error. Since, when the difference is 3 times the standard error, data are considered statistically significant, it could be concluded that the sample was large enough to establish the superiority of the 27 to 28 hour antigen over the antigen refrigerated for 15 minutes.

The 9 sera which failed to react with the 27 to 28 hour antigen suspension showed negative standard and presumptive Kahn reactions, and none of them gave more than a doubtful reaction with the 4 hour antigen. One serum which showed positive Kahn Standard and Presumptive tests and a doubtful Mazzini failed to react with the 15 minute refrigerated antigen.

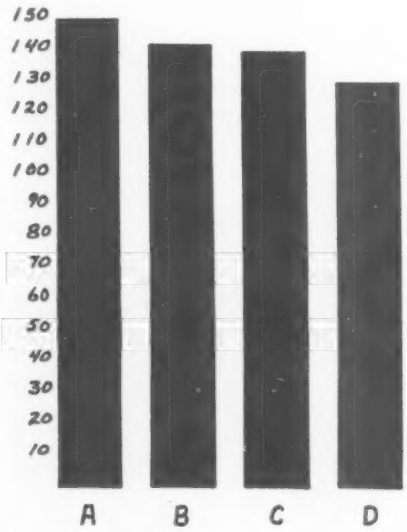

FIG. 2.—Comparison of antigens and number of reactions—summer series. *A*, 4 hour antigen; *B*, 27–28 hour antigen; *C*, antigen refrigerated 15 minutes plus one hour at room temperature; *D*, antigen refrigerated 15 minutes.

When the 27 to 28 hour antigen suspension and the antigen suspension ripened for 15 minutes in the refrigerator plus 1 hour at room temperature which failed to react 18 times (17.5%), were compared, the standard error of the difference was 4.8, and the number of standard errors contained in the difference was less than 2. Therefore, the sample was not large enough to establish the superiority of the 27 to 28 hour antigen over the antigen refrigerated for 15 minutes plus 1 hour at room temperature.

When the 27 to 28 hour antigen suspension was compared with the 4 hour antigen the standard error of the difference was 2.87, and the number of standard errors in the difference was more than 3. There-

fore, the conclusion could be drawn that the 4 hour antigen suspension was the most sensitive.

Summer Series. The same 4 types of antigen suspensions used in the winter were tested during the summer at room temperatures.

When the specificity of these antigens was compared, it was found that out of 133 sera reacting negatively with the 4 hour antigen suspension only 1 showed a doubtful reaction and that was with the 27 to 28 hour antigen suspension.

When the sensitivity of the 4 types of antigen suspensions was compared in the summer series it was found that 150 sera showed reactions with the 4 hour antigen suspension, 144 reacted with the 27 to 28 hour antigen suspension, 140 reacted with the antigen suspension refrigerated for 15 minutes and then allowed to stand 1 hour at room temperature, and 129 reacted with the antigen suspension refrigerated for 15 minutes. This is graphically illustrated in Figure 2.

When the sensitivity of the 27 to 28 hour antigen suspensions which failed to react 6 times (4%) were compared with the 15 minute refrigerated antigen suspension which failed to react 21 times (14%), the standard error of the difference was 3.25, and the difference in the two percentages was three times the standard error. Therefore, it could be concluded that the 28 hour antigen demonstrates statistically its greater sensitivity.

When the 27 to 28 hour antigen suspension and the antigen suspension refrigerated for 15 minutes plus 1 hour at room temperature which failed to react 10 times (6.7%) were compared, the standard error was 2.6. The difference was not 3 times the standard error; therefore, the difference in sensitivity is not statistically significant.

When the 27 to 28 hour and the 4 hour antigen suspensions were compared the standard error was 1.6. The difference was not 3 times the standard error, so that, although the indication was that the 4 hour antigen suspension was more sensitive yet statistically the difference is not quite significant. In a larger series this could probably be proved.

None of the sera failing to react with the other 3 antigen suspensions showed more than a doubtful reaction with the 4 hour antigen suspension.

Summary. After statistical analysis of the results, the following conclusions were drawn:

1. Mazzini antigen for routine use should be ripened 3 to 4 hours at room temperature.

2. Mazzini antigen which has stood at room temperature for 28 hours in the winter or even in summer heat up to 94° F. is more sensitive for emergency use than that ripened in the refrigerator for 15 minutes.

Acknowledgment is gratefully made to Mr. L. Y. Mazzini for his advice and to Mr. D. R. Cawthorne, of Miami University, for his statistical analyses.

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FURTHER EXPERIENCE WITH FURFURYL-TRIMETHYL-AMMONIUM IODIDE (FURMETHIDE) IN THE TREATMENT OF URINARY RETENTION DUE TO BLADDER ATONY*

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Some months ago, the treatment with furfuryl-trimethyl-ammonium iodide (Furmethide) of urinary retention due to bladder atony following surgery on the rectum was described.[5] It was concluded that this substance, a parasympathomimetic drug with strong action on the bladder, had certain advantages over such other drugs as mecholyl and doryl. Since that time, additional similar cases as well as instances of bladder atony due to a variety of other causes have been studied and treated under the described and modified régimes. The results have been striking enough to warrant publication of the data accumulated thus far. It was felt that these observations might be pertinent to the treatment of certain types of war casualties.

Material and Methods. Thirty-one patients have been studied. For purposes of discussion they have been divided into groups as follows: Group I. Patients who had operations at a distance from the bladder; Group II A. Patients who had operations with mild or moderate trauma to the bladder or its nerves; Group II B. Patients who had operations with severe trauma to the urinary bladder or its nerves; Group III. Patients with disease of the central nervous system.

In every case the volume of residual urine was measured immediately before the administration of the first dose of Furmethide and thereafter as indicated. Cystometric studies were also made. A number of the patients had previously received mecholyl or doryl in unsuccessful attempts to restore bladder function.

Observations. *Group I. Urinary retention in 8 patients following operations not involving the vicinity of the urinary bladder:* 2 patients after thyroidectomy, 2 patients after herniorrhaphy, 1 patient each after cholecystectomy, drainage of an abscess of the chest wall, ovariectomy and cecostomy. Six (75%) of the patients began to void normally after 1 or 2 doses of Furmethide subcutaneously. The 2 who did not void did sweat, salivate and/or lacrimate and had definite intensification of the desire to void.

Group II A. Urinary retention in 9 patients following slight or moderate trauma to the bladder or its nerves: 2 patients after delivery,

* This investigation has been aided by a grant from the Smith, Kline & French Laboratories.

2 after hysterectomy, 2 after colporrhaphy, 1 after fracture of the pelvis, 1 after operation on a hernia which contained the bladder, and 1 after operation on an appendiceal abscess which extended into the pelvis. Seven patients (78%) responded favorably.

Case Studies. Case 57865 illustrates the course in a successfully treated case. B.W., a 28 year old woman, was operated on for appendiceal abscess extending deep into the pelvis. A drain was left in place after operation. The patient could not void and required catheterization for the first 5 days after operation. Furmethide was then started in doses of 4 or 5 mg. given subcutaneously (Fig. 1). Voiding began after the second injection, with volumes of residual urine of 150 to 900 cc. initially. The next day, however, the volume of residual urine was less than 1 ounce. After 10 days of subcutaneous and oral administration of Furmethide, the patient was able to void without medication; there was only a small volume of residual urine.

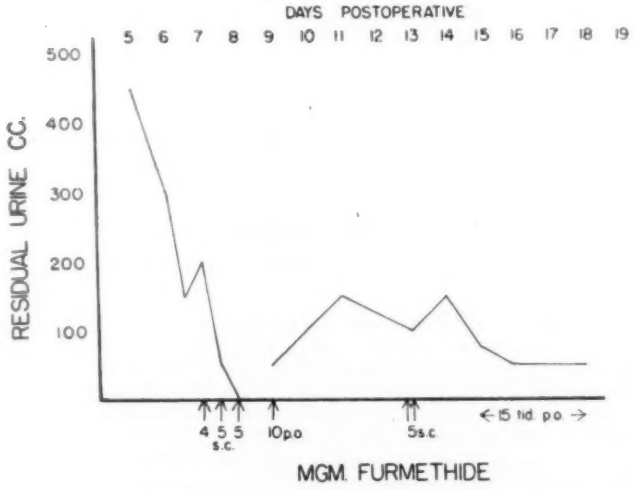

Fig. 1.—Case No. 57865. Appendiceal abscess.

Case 58958 illustrates the course in an unsuccessfully treated instance and demonstrates the cause of failure in this case. R.T., a 52 year old woman with a history of diabetes, was operated on for rectocele and cervical erosion. She could not void after operation and required catheterization. The administration of doryl had no effect on bladder function. Cystometric studies on the 6th postoperative day revealed an atonic bladder. The administration of 3.5 mg. of Furmethide subcutaneously while the catheter was in place caused prompt contraction of the bladder. During the next 4 days, however, the drug in doses of 5 to 10 mg. given subcutaneously resulted in no voiding or only slight emptying of the bladder, in spite of the presence of other evidences of the action of Furmethide, such as sweating and salivation. Cystoscopy on the 13th postoperative day revealed marked bullous edema of the vesical neck which was considered to be acting mechanically to prevent emptying of the bladder.

Group II B. Urinary retention in 6 patients following severe trauma to the bladder: after abdomino-perineal resections for carcinoma of the

rectum. All of the 6 patients (including 3 previously reported[5]) responded favorably. It is to be noted that none of the 6 patients responded favorably to the administration of Furmethide until after the pack was removed from the space formerly occupied by the rectum.

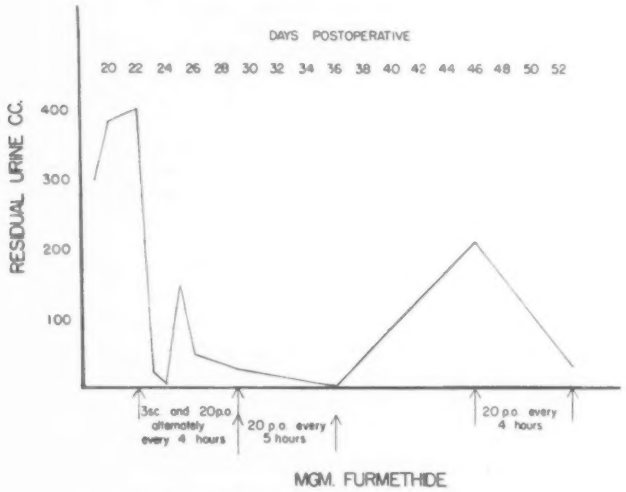
DAYS POSTOPERATIVE
20 22 24 26 28 30 32 34 36 38 40 42 44 46 48 50 52
RESIDUAL URINE CC.
400
300
200
100
3sc. and 20p.o. alternately every 4 hours
20 p.o. every 5 hours
20 p.o. every 4 hours
MGM. FURMETHIDE

Fig. 2.—Case No. 65139. Abdominal perineal operation.

Case 65139 (Fig. 2) illustrates the régime now in use in these patients. C.C., a 54 year old man, was unable to void after operation and was placed on constant drainage; his bladder was found to be infected. Constant drainage was discontinued on the 17th postoperative day, but the patient was still unable to void normally. Two days later he was given doryl, following which he voided 300 cc., leaving 300 cc. of residual urine. The next day the volume of residual was the same, after the voiding of 100 cc. following administration of doryl. Furmethide was started on the 22d postoperative day; the patient was given 3 mg. subcutaneously at 8 hour intervals and 20 mg. orally. Slight discomfort due to spasm of the bladder was noted on the first day, but not thereafter; moderate perspiration was the only persistent complaint. The volume of residual urine decreased rapidly. A week after the drug was started, the patient was discharged with orders to take 20 mg. by mouth at 8 A.M. and 1, 6 and 11 P.M. Seven days later the volume of residual urine was 0 cc. The drug was stopped for 10 days, after which the volume of residual urine was 210 cc. The drug was given again in doses of 15 mg. orally 4 times a day; at the end of a week the residual urine measured 50 cc. Increasing the dosage to 20 mg. by mouth 4 times daily caused a slight decrease in the residual urine volume to 30 cc. He still required the drug 54 days after operation.

Group III. Urinary retention in 8 patients with disease of the central nervous system: two instances of multiple sclerosis and one each of spina bifida, diabetic neuropathy, hydrocephalus, transverse myelitis due to metastatic carcinoma, vesical paralysis following operation for ruptured disk with spinal fusion at L5, and prolonged vesical paralysis following sympathectomy for hypertension. Seven of the 8 responded favorably.

Case 58720 (Fig. 3) illustrates the favorable action of the drug. M.E., a 45 year old woman, was found to have multiple sclerosis 12 years before admission to the hospital. Several months before admission for the treatment of uterine fibroids, urgency and frequency of urination, with the voiding of small volumes of urine, were noted. Supravaginal hysterectomy shortly after admission was followed by cessation of voiding, and constant drainage was instituted. Two weeks later cystometric study (Fig. 3) showed a pressure curve characteristic of the neurogenic bladder; the administration of Furmethide resulted in a normal cystometric curve. The volume of residual urine was 120 to 260 cc. before Furmethide was given. Administration of the drug in doses of 20 mg.

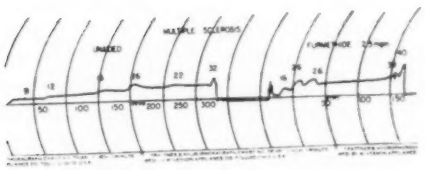

FIG. 3.—Case No. 58720. Multiple sclerosis.

3 times daily caused a decrease in the volume of residual urine to 30 cc. Reduction in the dose of 12 mg. 3 times daily was not followed by an increase in the volume of residual urine.

Case 57631 illustrates the unfavorable action of the drug. D.F., a 44 year old man, entered complaining of diarrhea, weakness of the legs and difficulty in voiding, the last progressing to complete retention a month before entry. Physical examination revealed absent knee, ankle and abdominal reflexes, atrophy of the leg muscles and poor tone to the rectal sphincter. The urine was full of pus. The spinal fluid contained 70 to 162 mg. per 100 cc. of protein as well as 0 to 5 lymphocytes per cmm. Constant drainage was instituted and sulfathiazole given; the urinary infection soon subsided. Cystometric studies revealed curves typical of the neurogenic bladder. The curves returned to normal after the administration of 3.5 mg. of Furmethide subcutaneously, desire to void occurring when the bladder contained 75 cc. of urine. Rectal and urinary incontinence became a complaint. The administration of Furmethide thereafter caused a reduction in the volume of residual urine, but aggravated the urinary incontinence. The rectal incontinence was not influenced.

Discussion. Furmethide (furfuryl-trimethyl-ammonium iodide) is related chemically to the other parasympathomimetic substances (Fig. 4). Several studies of its action in animals and in man are available.[2–6] Within a few minutes after the injection subcutaneously of

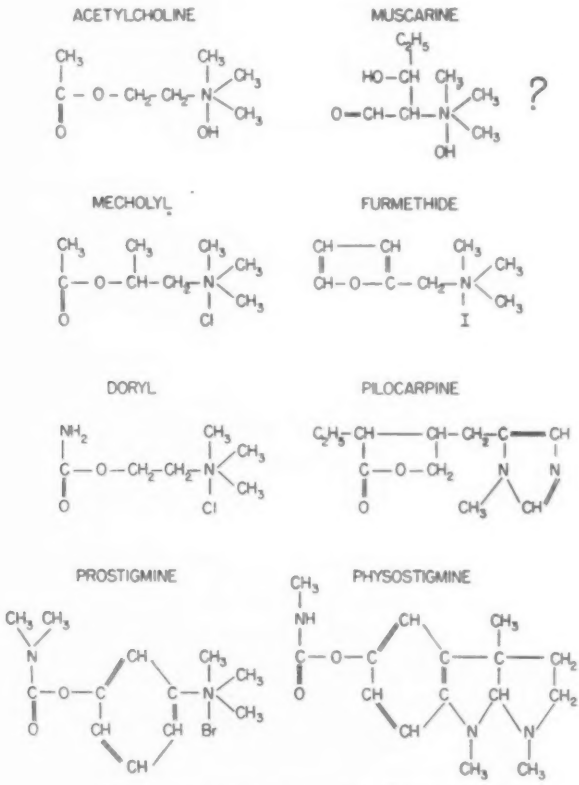

FIG. 4.—Chemical structure of Furmethide.

3 mg. or more in man, a diffuse flush, tachycardia, perspiration and salivation occur, varying in degree with the dose given. Simultaneously a desire to void is noted by the subject; cystometric evidence of increased vesical tonus[5] and roentgenographic evidence of contraction of the ureters and bladder[1] may be detected. With larger doses, transitory small decreases in blood pressure may occur; heart block has not been detected with the doses used.[2] The venous pressure is usually slightly elevated.[2] Visual accommodation occasionally may be disturbed.[2] Doses as large as 10 mg. given subcutaneously only rarely cause gastrointestinal symptoms; fluoroscopic and roentgenographic studies have revealed no change in the motility of the stomach, colon and gall bladder.[1] Uterotubograms show no evidence of contraction of the uterine or tubal musculature.[1] The administration by mouth of as

much as 30 mg. causes only sweating and an increase in vesical tonus. Compared to other commonly used parasympathomimetic drugs, Furmethide has relatively less action on the bronchi and cardiovascular system than mecholyl and on the gastro-intestinal tract than doryl and prostigmine. Its action on the urinary tract is much stronger than any of those drugs.

These pharmacologic studies in man strongly suggest that Furmethide is a useful drug in the treatment of the paralyzed bladder. Its striking effectiveness in the patients of Groups II and III above, in whom severe damage to the nerves innervating the bladder existed, is in harmony with this concept. It is also of interest that Furmethide was demonstrably effective in patients in whom doryl and mecholyl had previously been used unsuccessfully. The reason for its clinical effectiveness in the patients with bladder paralysis following operations distant from the bladder or with little trauma to the bladder, *i. e.*, Group I and some of Group II A, is difficult to determine. It is probable that in some of these patients, particularly those in Group I, normal bladder function would have returned spontaneously in one or a few days. Anesthesia (including spinal anesthesia), medication (including morphia and atropine) and abdominal pain may have been responsible for the urinary retention observed in these patients. The use of Furmethide in these instances merely served to initiate vesical contraction, following which the bladder resumed its normal function. Its action under these circumstances is useful in that it may obviate the need for catheterization.

Although the cases here reported illustrate the necessity for individual analysis, certain general rules may be formulated for the use of Furmethide. Patients with acute vesical retention of unknown etiology, occurring during infectious diseases or in the postpartum or postoperative state (Group I), are easiest to treat. Regardless of the nature of the factors responsible for the failure to void, if the bladder can be stimulated by a parasympathomimetic drug (Mecholyl, Doryl or Furmethide), the proper reflex pattern may be reëstablished and spontaneous voiding instituted. Furmethide will accomplish this purpose in such instances with fewer doses and greater percentage of certainty if the bladder is not allowed to become overdistended. As soon as it is ascertained or suspected that such a condition exists, and it is known that no obstruction is present, a dose of 3 mg. of Furmethide may be administered subcutaneously. Partial or complete evacuation of the bladder should take place within 5 to 10 minutes; if this dose is ineffective, the dose should be increased by increments of 1 mg. until 5 mg. is reached. If the patient does not void, or if it is felt that only partial evacuation has occurred, it is to be considered that the drug has failed to work and, accordingly, catheterization must be instituted.

Patients who have reversible organic damage to the bladder, its parasympathetic peripheral nerves or the central nervous system itself, require a different type of régime. Inability to void completely or at all in the absence of obstruction to bladder outflow and large volumes of

residual urine are characteristic of this group. Cystometric observation is helpful, but actually not required, preliminary to starting therapy. The immediate postoperative state is no contraindication to its use, although the reduction in efficiency of any therapeutic procedure should be anticipated in the first few hours postoperatively. The initial dose is 2 mg. in children and 3 mg. in adults; it should cause voiding within 5 minutes. If neither voiding nor sweating occurs, the dose is to be considered inadequate. Under such circumstances, the patient is catheterized and an increased dose is given in 8 hours or at desire to void, the dose being successively 4, 5 and 7.5 mg. If 7.5 mg. do not cause voiding of any urine, however little, the drug need not be used further. If voiding occurs, the patient should be catheterized for estimation of the volume of residual urine, and the drug given every 8 hours daily. Oral administration of the drug contemporaneously with giving it subcutaneously is more effective than the latter alone. A 10 mg. dose of Furmethide should be given orally 2 to 3 hours after each subcutaneous dose and should be increased by 5 mg. each dose until sweating is produced in 1 to 2 hours after a given dose. This dose is then continued indefinitely. The volume of residual urine after voiding following subcutaneous administration of Furmethide is the index of improvement of bladder tone and accordingly it should be measured at least once daily. Reduction of the volume of residual urine to less than 1 ounce usually requires 1 to 5 days. Once the volume of residual urine is 1 ounce or less, the question of continuation of the above régime is dependent on whether the underlying process is cured or not. In the usual patient with bladder atony following hysterectomy, therapy is needed for less than 10 days; after abdominoperineal resection of the colon and rectum for at least 4 weeks and sometimes indefinitely; and in such diseases as multiple sclerosis, indefinitely, or until remission occurs. In patients requiring prolonged administration of medication, it has been found possible after a time to use the drug orally only. If the combined type of treatment has been used previously in a given case, the effective oral dose for that individual, varying from 10 to 30 mg., is already established. If not, a few days of combined therapy is preferred to a complete transition from subcutaneous to oral medication. The drug, when given orally, may be administered 4 times a day (*e. g.*, 8 A.M., 1, 6 and 11 P.M.); a slight rise in the volume of residual urine may occasionally be anticipated incident to the change. If recovery of bladder tone has not proceeded far enough at the time of the change to oral therapy, uncomfortable sweating may be produced in spite of which the volume of residual urine may rise over that found during the period of subcutaneous administration; reversion to the latter for a longer period may be necessary. It is unnecessary to emphasize that the smallest dose, subcutaneous or oral, which will produce the required effect upon the bladder is to be used, once a given routine is established.

In patients with severe, permanent damage to the peripheral or central nervous control of the bladder, the drug must be given indefinitely. Cases of transverse myelitis, such as occur in wartime, fall into

this group, The anticipation of the necessity for indefinite use of large doses and the combined routes of administration, together with Credé manipulation of the bladder, are necessary in addition to the general approach outlined above.

The only side-reactions which thus far have proved troublesome have been perspiration and to a lesser extent salivation and lacrimation; vomiting occurred in one instance. These side-reactions are annoying, but not dangerous. After subcutaneous administration of the drug, sweating is more likely to be annoying than after oral medication. The body temperature may fall following profuse perspiration; the patient should be well covered at this time. In every patient studied, an amount of drug large enough to be effective, but too small to cause more than minimal discomfort has been found. The patients who experienced mild sweating consequent on taking the drug preferred it to the constant urinary drainage or repeated catheterizations which discontinuing Furmethide would mean.

The drug may possibly be contraindicated in patients with ulcer or bronchial asthma; our observations permit of no conclusions in this regard. It does not appear to be contraindicated in the doses suggested in hypertensives or in patients who have arteriosclerosis but no clinical evidence of heart disease; it may possibly act deleteriously in patients with overt cardiac disease. It has no untoward effects in patients with thyrotoxicosis. Furmethide cannot be expected to relieve urinary retention due to vesicle neck obstruction caused by caruncles, enlarged prostates, neurogenic spasm, post-traumatic edema, or a large pack placed in the space formed during an abdomino-perineal resection; its use is contraindicated in such instances. Severe bladder infection predisposes to spasm and its occurrence requires a preliminary period of perhaps 10 days during which tidal or constant drainage, as well as chemotherapy should be employed. Patients who have incontinence as well as atony of the bladder are usually made more uncomfortable by Furmethide.

Summary and Conclusions. 1. Furmethide (furfuryl-trimethyl-ammonium iodide), a parasympathomimetic substance with strong action on the bladder, has been used in the treatment of bladder atony caused by a variety of factors in 31 patients.

2. Urinary retention was relieved in most patients; the volume of residual urine in such instances was markedly reduced.

3. Side reactions, consisting of perspiration and salivation, were occasionally troublesome but never dangerous with the doses used.

4. Obstruction of the vesical neck constitutes a contraindication for the use of Furmethide.

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THE RAPID REMOVAL OF EXCESS JOINT FLUID BY ACID SALTS

EXPERIMENTS WITH TRAUMATIC HYDRARTHROSIS OF THE KNEE JOINT

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EFFUSIONS in the knee joint due to trauma are met constantly in the average general and industrial practice. The visible response to these traumata is not always an indication of their severity, as the synovial membrane may produce an enormous amount of effusion after some minor injury, or on the other hand very little fluid following a severe cartilage tear. Most of the knee injuries which result in more or less massive effusions consist of ligamentous sprains without demonstrable gross tearing or cartilage injury.[5] In any individual case, it is of course important to rule out by Roentgen ray any possibility of an intra-articular knee fracture.

For the past year experiments were under way to see if it was possible to reduce the amount of joint fluid in these cases of traumatic hydrarthrosis by a low salt, acid-producing diet, and by giving adequate dosage of ammonium chloride, in a similar manner to the removal of other forms of obvious or occult edema fluid. Of the 7 cases to be described, 1 was treated by salicylates, Ace bandage compression and short-wave therapy; another patient could not take ammonium chloride because it induced abdominal cramps; another had to be tapped on 3 occasions; and the others benefited in a rather marked way from the therapy to be discussed. This consisted of a low sodium chloride-acid forming diet, without restriction of fluids, and ammonium chloride in daily doses of 90 gr. (6 gm.), bed rest, and application of an ice cap to the involved knee. The last 3 cases can be used as controls, as they did not have the prescribed régime. Recently also, it was demonstrated that it was possible to increase or decrease the joint fluid in certain cases of rheumatoid arthritis by giving the patient adequate amount of bicarbonate of soda or alternatively ammonium chloride.[3]

Anatomy. The pertinent anatomy of the knee joint can be briefly summarized. There are two cruciate ligaments preventing forward and backward displacement of the knee joint. However, the muscles surrounding the joint, *i. e.*, the quadriceps and its tendon, the hamstrings and the gastrocnemius really insure stability of the knee joint.

Physiology. The synovial fluid has been the subject of much recent experimental work. Certain conclusions may be drawn from these researches.[1,7]

The synovial fluid has an exceedingly close connection with the blood stream. If glucose is taken by mouth it reaches the knee joint very rapidly. It has been shown experimentally that particulate matter can be removed from the synovial fluid by phagocytosis of leukocytes and macrophages. Absorption may take place through

the capillaries or through the lymphatics of the synovial membrane. Isotonic solutions are easily absorbed from the synovial capillaries. Heavier solutions are absorbed more slowly. The synovial membrane is divided into two portions: the villus type covering the folded areas, which has in villi synovial cells that are filled with mucin; and the non-villus type that covers the smoother areas. The synovial fluid is formed principally from lymph plasma from the capillaries of the synovial membrane, plus mucin from the synovial cells. Allison and Ghormley[1] summarized the subject well when they stated that the synovial membrane is derived from the mesenchyme, that it can regenerate, that it has the power of secreting a fluid mainly derived from the blood plasma, but modified by mucin, and that certain cells may be found in the synovial fluid which are for the most part phagocytes, and help in removing the particles from the joint.

Case Reports. Case 1. F. C., female, age 45, salesgirl, fell and injured her left knee during a snowstorm. Soon after, the left knee measured 34.2 cm. and the right 32 cm. in circumference at the mid-patella level. There was marked limitation of motion. Bed rest and an ice cap was advised for 5 days, without any change in either the measurements or in the mobility of the knee. Then the patient was put on ammonium chloride, 6 gm. (90 gr.) daily in divided doses, and a low sodium, acid-ash diet. Fluids were not restricted. After the 3d day, the reduction in circumference of the injured knee was at the rate of approximately 0.5 cm. a day, so that by the end of 7 days, the involved knee was but 0.5 cm. larger than the normal knee. The range of motion at this time was complete, and the patient was allowed out of bed for short periods of time. Ace bandage compression was applied throughout this period. The patient was soon able to return to work.

Case 2.—J. B., male, age 20, college athlete, injured his right knee in a basketball game. Although the knee began to swell immediately, he completed the game and went to classes the following day. That evening, examination revealed a tense, immobile right knee measuring 40.3 cm. in circumference at the mid-patella level, as against 36 cm. for the left (uninvolved) knee. The patient was put to bed and an ice cap was applied to the knee. After 2 days, in which the knee had not decreased in size or changed in mobility, an orthopedic consultation was arranged. Tapping was advised, and 90 cc. of xanthochromic fluid was obtained. A tight bandage was applied and a posterior moulded splint. Within 12 hours the fluid had reaccumulated in the joint, the temperature had risen to 103° F., and the patient was hospitalized. Here the joint was tapped again and 150 cc. of bloody fluid was evacuated. A circular cast was applied for 2 weeks; the knee had shown no tendency to reaccumulate fluid at that time.

Six months after this event, the patient again injured his right knee by twisting it. As before, the part began to swell, but this time he went to bed. An ice bag was applied, but there appeared to be no results as far as diminution of the swelling in a 3 day period. Examination at this time revealed a tense, swollen, immobile right knee measuring 40.5 cm. in circumference; the left knee, 36 cm. The patient was put on a low sodium, acid-ash diet, and was given ammonium chloride, 6 gm. daily in divided doses. Fluids were not restricted. After the second day the size of the involved knee decreased, and the part became more mobile. One week later, the involved knee measured 36.6 cm. (a diminution of 3.9 cm.) and the mobility was normal. At this time the patient had to take his final term examination, and went to school in spite of medical objections. Compression by Ace bandage was used while the patient was ambulant. There was no recurrence of the hydrarthrosis.

Case 3. J. L., age 20, civilian Red Cross worker, twisted his left knee while playing soft-ball. The knee began to swell almost immediately. On

examination the left knee measured 39.5 cm. in circumference at the mid-patella level; the right knee, 36.5 cm. The involved knee was tense. The patient was immediately placed on a low sodium, acid-ash diet without limitation of fluids. Ammonium chloride was used in the amount of 6 gm. (90 gr.) daily in divided doses. There was remarkably prompt improvement, the knee becoming more mobile on the first day after therapy was started. At the end of 1 week, the involved knee had returned to normal (36.5 cm.) while the mobility had increased to almost normal range. Compression by means of an Ace bandage was applied and the subject was allowed to become ambulant.

CASE 4. A. R., age 25, female, maid, injured her left knee by striking it against a table while at work. When first seen several hours later, the left knee measured 39.6 cm. in circumference, as against 36 cm. for the right (normal) knee. The patient was ordered to bed but refused, so that the treatment was largely ambulant. A low sodium, acid-ash diet was detailed and ammonium chloride tablets (90 gr.) a day in 4 divided doses was ordered. Fluids were not restricted. The swelling decreased rapidly while the mobility increased. At the end of 6 days the left knee measured 36.5 cm. (0.5 cm. more than the normal knee). Reëxamination at the end of 8 days revealed the left knee had returned to normal size (36 cm.). There was no return of the swelling.

CASE 5 (Control). J. W., age 45, male, baker, hit his left knee against a machine with great force. The knee began to swell within several hours and the patient left the plant with great difficulty. On examination the left knee was markedly swollen, measuring 40 cm. in circumference at the mid-patella level; right knee, 37 cm. There was extreme difficulty in bending the knee. Paracentesis was advised but was refused, and therefore bed rest, salicylates, and an ice cap to the knee was prescribed for 5 days. During this time there was no decrease in the size of the involved knee. Short-wave therapy with a 12 meter portable machine was given every other day at the patient's home. At the end of 4 weeks, there was a decrease of 1.5 cm. in the circumference of the left knee, and the movement was improved. At this time the patient was allowed out of bed with Ace bandage compression to the knee and the short-wave therapy was continued. At the end of 8 weeks the left knee still measured 38.5 cm. in circumference (1.5 cm. more than the other knee) although movement was adequate, and the patient had therefore returned to work.

CASE 6 (Control). M. B., female, age 40, chambermaid, fell down several stairs striking her left knee. She continued working even though her knee began to swell and continued to swell. The patient refused to stop work and was ambulatory throughout her course of therapy. Examination revealed that her left knee measured 37.2 cm. at the mid-patella level; right knee, 33 cm. A low salt-acid ash diet and ammonium chloride was prescribed, but could not be continued because of severe abdominal cramps. Short-wave treatment and Ace bandage compression was used throughout the treatment. At the end of 4 weeks of care, flexion and extension were still difficult, but were improved over the original state. The measurement was 36.5 cm. for the left knee at the mid-patella level, a diminution of 0.7 cm. At the end of 7 weeks, the left knee was considerably more mobile, although its circumference was 35.5 cm., 2.5 cm. more than the uninvolved knee. At this point contact was lost as the patient went to California.

CASE 8 (Control). J. K., age 40, male, paperhanger, injured his right knee when he struck it against a wall. When seen 2 days afterward, the right knee measured 40.2 cm. in circumference; left knee, 37 cm. Paracentesis yielded 95 cc. of a xanthochromic fluid. The measurement following this was 37.5 cm. for the right knee. An Ace bandage was applied for compression. Four days later, the fluid had reaccumulated, and the involved knee measured 40.8 cm. Again tapping was resorted to, with the removal of 85 cc. of joint fluid. The measurement following this procedure was 38 cm. However, in 3 days the joint fluid again reaccumulated (measurement 40 cm.). This time after tapping a snug plaster cast was applied to the right joint. After its

removal in 10 days, there was but slight reaccumulation (measurement 38 cm., *i. e.*, 1 cm. more than the uninvolved knee). Thereafter an Ace bandage was applied, and short-wave therapy was given every other day. Ten days later (*i. e.*, 29 days after the injury) both knees measured 37 cm. in circumference and treatment was stopped.

Comment. The diagnosis of traumatic hydrarthrosis (traumatic synovitis) of the knee with effusion is relatively easy. A direct or indirect injury to the knee, occasionally even a moderate twist, may cause a profuse outpouring of synovial fluid, and therefore a great swelling of the joint. This occurs without a cartilage tear or interarticular fracture, although these conditions must be carefully excluded before assuming that the more benign state exists. The synovial fluid in a traumatized joint is said to contain large numbers of erythrocytes, a variable white cell count, an increased amount of bilirubin (due to red blood cell hemolysis), and mucin. The icteric index of synovial fluid in traumatic effusions is usually above 5; on the other hand in the effusion of inflammatory arthritis the icteric index is below 5. The only other conditions causing increased bilirubin content of the synovial fluid consists of the hemarthrosis of hemophilia, sarcoma, xanthoma and tabetic arthropathy.[2]

The treatment of hydrarthrosis as usually carried out consists of an aspiration of the excess joint fluid, with the application of a tight adhesive plaster or plaster-of-Paris bandage, and rest for a period of several weeks. Not infrequently the fluid has a tendency to recur. The necessity of careful paracentesis must be stressed. Carelessness may result in the serious complication of suppurative arthritis, or as happened in one of the cases described, a hemarthrosis. Titus[9] treated an unusually large number of these cases with the static electric current, and he claimed a marked diminution of the extravasated fluid following several treatments. I have no familiarity with this form of treatment.

The effect of injested alkali on the content of joint fluid has been the subject of a recent communication.[3] The authors were able to increase the joint fluid in a case of rheumatoid arthritis by feeding sodium bicarbonate and to decrease the fluid by a low sodium diet and ammonium chloride in full doses. In our study of traumatic hydrarthrosis, strict attention was paid to the diet (see Table 1) which should be of low sodium content and preferably contain acid forming foods or, at least, be so selected that the combustion of foods would release as much acid as base. Salt in any form is interdicted. Fluids are not restricted. The rationale of this method of edema fluid removal was first enunciated by Newburgh,[4] but has recently been so clearly and succinctly stated by Schemm[8] that it bears repetition (almost but not exactly *verbatim*).

Edema fluid is a simple increase of interstitial fluid, and it can accumulate only if the materials that it holds in solution have been retained. For each 2 pounds of edema fluid, these consist of 10 gm. of an alkaline mixture of sodium salts (5 parts of sodium chloride and 1 part of sodium bicarbonate), and 1000 cc. of water as a solvent for

these salts. This alkaline edema fluid remains indefinitely, unless the bicarbonate fraction of sodium salts is used up by the acids formed from metabolism or by the injection of acid substances. Acidification causes the kidney to overcome this threat to the pH of the body fluid by elimination of the neutral or acid salts, or as it is usually expressed: acidification mobilizes the sodium of the body. As the sodium leaves the body by way of the kidneys, its water of solution is free either to leave the body as urine water, which causes weight loss and diuresis; or to leave the body as water vapor, thereby causing

TABLE 1.—AN ILLUSTRATIVE DIET LIST[a]

Breakfast

Fruit: Prunes, stewed figs, plums, other fruits only sparingly.
Cereal: Oatmeal, puffed rice or shredded wheat or farina with cream.
Eggs: Eggs., any style.
Breads: White toast or muffins or French toast.
Beverage: Coffee, or tea with cream.

Lunch

Fruit: Prunes (plain or juice) or cranberry sauce.
Meat or Fish: Choice of: beef, chicken, liver, mutton, pork, rabbit, veal; cod, haddock, halibut.
Vegetables: Corn or lentils (other vegetables must be used sparingly with this diet).
Salads: Prune and cottage cheese salad.
Breads: White bread or white flour muffins.
Beverage: Coffee or tea with cream.
Dessert: Nuts may be eaten as often as desired.

Dinner

Soup: Meat stock soup, preferably without vegetables. (They may be used in moderation only.)
Meat: Choice of meats or fish (as above in *Lunch*).
Eggs: Eggs, any style, may be substituted in the meal.
Vegetables: May be taken in small amount but should be buttered. Corn or lentils may be taken as often as desired. Peas and onions should be eaten less often. Spaghetti and macaroni are especially good.
Cheese: Cottage cheese salad, cheese in all forms are desirable.
Beverage: Coffee or tea with cream or sugar.
Dessert: Cranberries, plums and prunes are the only fruits allowed in unlimited amounts.

NO SALT TO BE USED IN COOKING OR AT THE TABLE

weight loss without diuresis; or to remain within the body to remedy cell dehydration giving a shift of water to the cells, causing the disappearance of the edema without weight loss or diuresis. This sodium then leaves the body *via* the kidneys in solution as urine. The water reaches the kidney only if all the demands of the body are met, therefore sufficient water must be supplied so that enough water will reach the kidneys for the elimination of the sodium.

The salutary effect of the use of the low sodium-acid or neutral ash diet coupled with adequate dosage of ammonium chloride (90 gr.

(6 gm.) per day) in the removal of the effusion in traumatic hydrarthrosis is worth reporting. The reasons given for not restricting fluid, paradoxical as it may sound, are good and sufficient. It cannot be claimed that a new treatment exists for the removal of effusions in the joints on the basis of the few cases described. Rather it is interesting from an experimental viewpoint, and substantiates fully the report of Jacobson, Leichtentritt and Lyons[3] in their attempt to influence the volume of joint fluid in rheumatoid arthritis.

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THE EFFECT OF ERGOTAMINE TARTRATE AND NEOSYNEPHRIN HCl ON THE WORK CAPACITY OF HUMAN MUSCLE*

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One of the minor complications of ergotamine tartrate therapy of migraine headache is the occurrence of occasional muscle cramps and weakness. O'Sullivan[3] states, "Thirty-seven (out of 97) of our patients complained of generalized weakness associated with the migraine attack. Fifteen individuals stated that after the alkaloid had eliminated the headache their legs felt tired and weak. It is rather difficult to determine whether this asthenia was caused by the drug or whether it was a coextent migraine phenomenon that the drug was unable to eliminate. A few of the patients state with certainty that this 'all in'

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feeling is more noticeable to them after the drug than before." This weakness was sufficient in one of her patients to cause a serious fall. The purpose of our study was to determine, if possible, whether therapeutic doses of ergotamine tartrate would consistently produce muscle weakness in normal individuals. Experiments on neosynephrin HCl were also performed as a control to the subjective and blood pressure effect of the ergotamine tartrate.

Method. The Maison ergograph[2] was used to the point of fatigue to measure the work capacity. With this ergograph the extensor digitorum communis of either arm may be worked at a constant stroke rate and with a measured, uniform stroke. It has the advantages that no other muscles can be used to apply force to the work, the initial application of the hand is uniform because of the easily found landmarks, and the extensor digitorum muscle is otherwise little used in everyday life. The muscles were voluntarily contracted once each second, lifting a load sufficient to produce fatigue in 2 to 4 minutes. When, as a result of training, the subject could lift a given load for 10 full minutes, an increased load was applied in order to return the subject to the experimental range. As a training and stabilizing influence, the subjects exercised each arm daily for a fixed period of 10 minutes with a light load.

Ten thoroughly trained subjects were used after a training period which varied from 3 to 14 months, during which time the muscles of each arm were worked to fatigue 6 days a week. The load was increased by 300 gm. when a given subject was able to carry the previous load in steady state (10 minutes). Since the subjects frequently had greater variation in work output when working with an "easy" load, they were drug tested whenever possible 1 or 2 weeks after starting a new and heavier load. The 10 subjects used were male medical students and the authors. Two of these subjects had occasional periodic migraine headaches.

The recipients were not aware of the nature of the injected drug, and hence, placebo injections could be interspersed according to a prearranged schedule. The injection was usually made at 11 A.M. after a light breakfast. The work ability was tested at the height of drug action 90 minutes after the intramuscular injection of $\frac{1}{4}$ to $\frac{3}{4}$ mg. doses of ergotamine tartrate, or 15 to 30 minutes after 4 to 10 mg. intramuscular doses of neosynephrin HCl. The subjects were assigned to work either 30 or 90 minutes after the placebo injections of hypotonic saline. The subjects were seldom used oftener than once a week.

The data were graphed as deviations from the mean in fractions of the standard deviation calculated by using the 5 or more previous work periods and an equal number of subsequent work periods as the control period. The work outputs in kg./cm. of the left and right hands were first averaged and the standard deviation of these 10 or more data determined. The deviation from the mean of the averaged left and right hand work output on the experimental days was then compared to the standard deviation and expressed as a fraction or multiple of this deviation. By this method of calculation the gradual increase in work output which occurs in all training subjects was given equal weight both before and after the test day, and the calculation minimized the danger of recording any chance increased work output as a drug effect. While in the usual statistical treatment of biologic data any increase or decrease in work output beyond two standard deviations can be considered significant, in our treatment of the data we are comparing a single determination with a mean. Hence, this 2 S.D. rule can be applied only to the final mean for each drug.

Results. The data are summarized in the scatter graph, Figure 1. In general, no significant decrease in work output occurred after the intramuscular injection of ergotamine tartrate. The 3 decreases

greater than 2 S.D. did not occur twice in the same individual, for each of these subjects was given 2 injections of ergotamine tartrate. The mean of the work output in 21 trials on the 10 subjects was −.55 standard deviations (S.E. of mean = .26), which was less than the mean for either the placebo injections or the neosynephrin HCl injections. The work capacity after the placebo injections varied from one negative standard deviation to 1.9 standard deviation plus. The mean for the 15 trials was +0.36 standard deviation (S.E. of mean = .25). This slight increase must be attributed to the psychic effect of the injection. In the case of neosynephrin HCl the work output after intramuscular injection of 5 to 10 mg. was marked in 2 instances and above 2 S.D. in 6 out of 20 trials. The mean increase was also

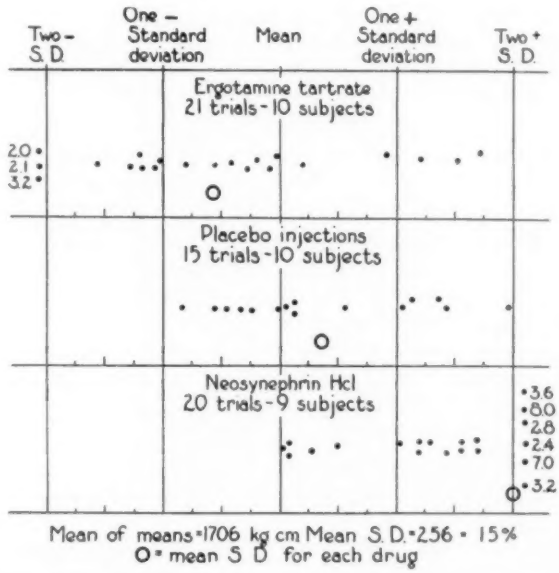

FIG. 1.—Scatter graph of work output of the 10 trained subjects. The work output on the test day is graphed as a fraction of the S.D. determined by analysis of the preceding and subsequent data. One mean S.D. is equal to 256 kg. cm. or a 15% change in work output.

significant, being 2.04 standard deviations (S.E. of mean = 0.15). Two of the subjects had periodic migraine headaches, and the mean of their calculated work output after ergotamine tartrate was −1.47 standard deviation. However, their average effort with the placebo injection was −.29 standard deviation and only +.05 with the neosynephrin HCl injection. Thus, they were relatively low in all experimental drug trials of work output.

Subjective symptoms from ergotamine tartrate were surprisingly few even with doses of $\frac{3}{4}$ mg. The subjects reported slight nausea, masseter trismus, slight dizziness, and occasional sweating. No vomiting occurred. The 2 migraine subjects noted that the subjective effect of ergotamine tartrate was much less than those symptoms elicited

by an equal dose of the drug at the time of a headache. Occasional symptoms elicited by neosynephrin HCl were pilomotor activity and frontal headache of short duration. The maximum slowing of pulse rate occurred 30 minutes after neosynephrin HCl, and this was taken to be the time of maximum drug action.

Discussion. By far the most significant finding of this study was the increased work capacity after the intramuscular injection of neosynephrin HCl. Since this drug is sympathicomimetic and chemically similar to epinephrin, one might, according to the emergency theory of epinephrin action, expect an increase in work output. However, a search of the literature has failed to reveal any exact studies of the work capacity in trained subjects after epinephrin injections. These data must, hence, stand without comparison to epinephrin data.

The effect of an injection of any kind has always been given a high psychic value by cautious experimenters when the data have not been or cannot be subjected to statistical analysis. The findings in this study that injection of a placebo results in only a +.36 S.D. mean rise in work output speak for the intense endeavor and stability of our subjects. The data also indicate that in normal subjects, at least, the psychic effect of a simple injection has been hitherto overrated.

Finally, when the effect of the smooth muscle stimulant, ergotamine tartrate, is compared with the smooth muscle stimulant, neosynephrin HCl, the failure to obtain an increase in work output with ergotamine tartrate may be significant, since they were used in doses which produce proportionate rises in blood pressure.[1-4] By this comparison the ergotamine tartrate effect to slightly decrease work capacity assumes possible significance. However, the only definite conclusion to be drawn at present must be that muscle weakness occasionally encountered clinically in treated migraine patients cannot be due to the direct action of ergotamine tartrate. Some predisposing factor in the migraine syndrome must potentiate the slight effect of ergotamine tartrate on striated muscle.

Summary. The work capacity of a group of trained subjects was:

1. Decreased (but probably not significantly so) by intramuscular ergotamine tartrate.
2. Slightly increased by intramuscular placebo injections.
3. Significantly increased by intramuscular neosynephrin HCl injections. The muscle weakness occasionally reported from ergotamine tartrate of migraine headache cannot be due entirely to the drug. Some predisposing migraine factor must be involved.

The authors are indebted to the Sandoz Chemical Works, Inc., for the supplies of ergotamine tartrate and to the F. Stearns Company for the neosynephrin HCl used in this study.

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CARDIAC ARREST BY THE ACTION OF POTASSIUM*

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The earliest report of potassium poisoning in nephritis is that by W. G. Smillie in 1915 from the medical clinic of the Peter Bent Brigham Hospital.[20] He described a temporary episode of collapse with vomiting, following the administration of 10 gm. of potassium chloride as a diuretic. The patient had been diagnosed as having chronic nephritis with uremia. Smillie approached the problem experimentally on the basis of Reid Hunt's unpublished observation of the toxicity of orally administered potassium salts for nephrectomized guinea pigs, and found that 1 gm. of potassium chloride orally was quickly fatal to rabbits with nephritis induced by uranium nitrate.

In view of more recent knowledge of the action of potassium it is evident that the reaction of Smillie's patient illustrates an irritating effect of this substance acting locally on the gastro-intestinal tract.[30] At the same hospital new methods of investigation have since made possible a demonstration of the toxic effect of accumulated potassium ions in the body.

Toxic effects of potassium had been suspected previously in a variety of conditions,[19,26] but there was no way of demonstrating whether or not they had actually occurred. The recent development of exact micro-methods for the determination of serum potassium and the discovery of a specific sequence of electrocardiographic changes accompanying progressive elevation of the serum potassium in dogs[31] has made it possible to establish conclusively that in the first of the 2 cases described here, cardiac arrest resulted from an elevation of the serum potassium.

A search through the collection of electrocardiograms (ECG) of Dr. S. A. Levine subsequently revealed a similar tracing. This was from a second patient who also demonstrates the characteristic ECG and the final stages of the clinical course of potassium poisoning, although no potassium determinations were made.

Case Studies. Case 1. Med. rec. No. 61888. *Oliguria and azotemia, failure of adequate urinary potassium excretion, characteristic ECG changes of potassium poisoning, and a terminal flaccid quadriplegia.*

C. C., a 39 year old married negro painter, entered the Peter Bent Brigham Hospital on April 26, 1942, complaining of abdominal distress and nausea accompanied by a diminishing output of urine. He had been examined in the dispensary 13 months before entry because of low back and leg pain following

* This work was done under the auspices of the University Committee on Pharmacotherapy.

an automobile accident. At this time the blood pressure was 160/110. The urine was normal microscopically and had a specific gravity of 1.022. The spinal fluid was normal. Four months prior to entry when he was examined for government employment, the blood pressure was 160/90. The job which he undertook in apparently good health consisted of repair work and painting in a shipyard, an occupation which was not new to him. He had first become an apprentice painter in 1915, at the age of 12.

A month after he had started work, he began to take time out for sickness. For 3 months he had general malaise and occasional vomiting. In the last 3 weeks there was also a mild recurrent peri-umbilical pain. The discomfort gradually increased up to the 5th day before admission. On that day there was return of the numbness in the left leg which had occurred at intervals since his automobile accident 19 months before. While at lunch on that day he experienced a severe exacerbation of the abdominal pain, accompanied by emesis and diarrhea. He also had a shaking chill with fever of 103° F. In the 4 days prior to admission no more bowel movements occurred, but vomiting and anorexia continued. At the same time the abdominal discomfort gradually improved. He described the urine as deep amber in color and amounting to only a pint a day for 4 days.

Physical Examination. The patient was a well-developed negro who appeared comfortable but complained of feeling tired. He had a temperature of 99° F. by mouth. The ophthalmoscopic examination revealed minimal arteriovenous nicking of the retinal vessels. His heart sounds were of good quality and regular with a soft systolic murmur at the apex. The heart rate was 90 per minute and the blood pressure was 165/95. The abdomen was somewhat tense and rounded, but there was no tenderness of the costovertebral angle and only slight peri-umbilical pain on deep pressure. He had no peripheral edema. The tendon reflexes of the extremities were present and equal bilaterally.

Laboratory Data. The blood Hinton and Wassermann reactions were negative. The hemoglobin concentration was 12.6 gm. per 100 cc. and the hematocrit 43%. The white cell count was 9500, with a normal differential. A special search revealed no basophilic stippling of the red cells. The blood urea nitrogen was 91 mg. per 100 cc. on the day of entry and gradually rose to 141 at the time of death. On the 3d hospital day the non-protein nitrogen of the serum was 137 mg. per 100 cc. The total serum protein at this time was 6.6 gm. per 100 cc., of which 4 gm. were albumin and 2.6 were globulin. The icteric index was 8. Serum collected 24 hours before death contained 8.85 m.eq./l.* of potassium, and a specimen obtained a few moments after death contained 10.50 m.eq./l. of potassium.

The urine was turbid, amber colored, and had a specific gravity ranging from 1.008 to 1.012. The albumin content was 3+ by the heat and acetic acid test, and there were many red cells and white cells in the centrifuged sediment. After standing with added HCl the urine developed a rosy tint, but contained no porphyrins. The 425 cc. excreted during the last two days of life contained 20.6 m.eq. of potassium per liter. A stool specimen obtained by enema appeared normal and contained no occult blood.

Hospital Course. During the 6 days in the hospital he was afebrile, but remained in bed feeling nauseated, anxious and weak. He had to be urged to eat, and there were repeated episodes of vomiting. Despite an intake of 13,870 cc. of fluid orally and by vein, which averaged nearly 3 liters a day for 5 days, the entire output of urine amounted to less than 2 liters of 300 cc. per day during this period. He was also continuously constipated.

A 5 A.M. on the 5th hospital day, 24 hours before death, he experienced difficulty in reaching for the bell cord to call for a urinal. Immediately thereafter he lost all power to move the extremities except for an occasional slight flexion of one or two digits. However he was able to void at this time and again on a subsequent occasion.

* Milliequivalents or millimols per liter. (To convert to milligrams per 100 cc., multiply by 3.9).

With the advent of paralysis he became frightened and anxious, but experienced no pain. The extremities became cold and wet, and the tendon reflexes could no longer be elicited. Yet there was no paralysis of the head or trunk muscles and his mental faculties remained clear. At one time there were slight twitches about the mouth and the jaw jerk was hyperactive. No sensory disturbances were observed at any time. A lumbar puncture revealed no abnormalities of the spinal fluid.

The paralysis was accompanied by transitory episodes of bradycardia, but the blood pressure remained high and the pulse quickly returned to the usual rate of about 80 per minute. The ECG 4 hours after the onset of paralysis (Fig. I *A*) showed absent P waves, widespread intraventricular block, regular rhythm and a rate of 63 per minute.

Toward the latter part of the day there was evidence of some degree of recovery. By evening he was able to move his arms freely, but there was still weakness. The left knee jerk returned temporarily. He also recovered some use of the thigh and calf muscles, and could wiggle his toes slightly. At 10:45 P.M. he received 4.5 gm. of potassium chloride by mouth, on the possibility that the paralysis might be akin to familial periodic paralysis and would respond similarly.

However, by 1 A.M. the paralysis was again worse. The heart sounds were regular, with the same systolic and a new diastolic murmur at the apex and a reduplication of the second sound in the pulmonic area. The ECG at this time showed an even wider spread of the ventricular complexes (Fig. I *C*) than was seen on the first record. The pulse repeatedly slowed momentarily from rates of 60 or 80 to 20 or 30 beats per minute. At 5:45 A.M., after a sleepless night, he felt fatigued but was conscious and well oriented. The pulse rate was 74 and the quadriplegia had returned.

During the last hour of life ECGs were recorded almost continuously. The cardiac rhythm remained regular until about 15 minutes before death (Fig. I *B*), when momentary pauses began to appear after every third and then after every second beat (Fig. II *D*, *E*, *F*). A few moments before death he became drowsy, asked to have the bedclothes pulled away and wanted to have his hands rubbed. They had become colder and wetter. His speech was thick, and he seemed increasingly apprehensive, yet even at this time voluntary elevation of the head from the pillow was accompanied by a strong contraction of the abdominal muscles.

On the ECG, lengthening periods of asystole (Fig. II *G*) were interrupted by intervals of acceleration of the pulse to the original rate of about 80 per minute. Transitory intervals of ventricular fibrillation (Fig. II *H*, *I*) were followed by increasing periods of asystole interrupted by varying abnormal beats (Fig. II *J*; Fig. III *K*, *L*, *M*). After a very long asystole at 6:45 A.M. (Fig. III *N*) he became cyanotic and respirations ceased except for a few sporadic efforts. Two intracardiac injections of 1 mg. of epinephrin in water were followed by fibrillation of the ventricle (Fig. III *O*) but no heart sounds were heard and no peripheral pulse was felt. Each time, after the injection of 1 gm. of magnesium sulfate in water, the fibrillation ceased and single efficient cardiac contractions occurred. Heart sounds could be heard and pulsations could be felt at the wrist, but this activity was infrequent and soon died out. Artificial respiration was administered, but at 7:10 A.M., 25 minutes after the cessation of spontaneous respiration, fibrillary motion of the heart ceased entirely and there was no further response to epinephrin.

Autopsy. There were 300 cc. of clear fluid in the right pleural cavity and 200 cc. in the peritoneal cavity.

The heart was noticeably dilated and weighed 470 gm. Microscopically, there were some tiny scattered areas of myocardial fibrosis and atrophy, in a few of which were fibroblasts, lymphocytes and rare erythrocytes. The blood-vessels were normal.

The abdominal viscera were engorged, the liver, which weighed 1580 gm., appeared normal except for prominence of the lobular markings. Microscopic examination revealed atrophy and loss of liver cells in the pericentral areas.

This was accompanied by small deposits of lipoid material and a number of mononuclear cells containing brownish pigment.

The kidneys were enlarged and weighed 310 and 380 gm. The capsules stripped easily. On cut sections the architecture was well preserved but there was some bulging of the parenchyma. The microscopic sections showed edema, a chronic type of cellular infiltration of the interstitial tissue and degenerative changes in the epithelium of the renal tubules with occasional evidence of regeneration. There was very little abnormality of the vessels or glomeruli.

In the brain there was flattening of the convolutions of the cortex, but otherwise nothing grossly or microscopically abnormal in it or the upper cervical cord. No significant changes were found in other organs.

Discussion. This patient does not exhibit the usual syndrome of uremia as seen in the terminal stages of chronic renal disease. The completeness of the renal failure is reflected in the water retention, the fixed specific gravity and the rapid increase in the blood urea nitrogen, and even more significantly in an almost complete retention of potassium. Except for the paralysis, the clinical course of this patient corresponds closely to the observation of the rapid onset of collapse and death in dogs dying of spontaneous potassium intoxication after bilateral ligation of the ureters.[10]

In spite of blood levels between 8.85 and 10.5 m.eq./l. there were only 0.32 gm. of potassium in the 425 cc. of urine excreted in the last 48 hours. Calculated on this basis, 0.23 gm. of potassium were excreted in 300 cc. of urine each day for the last 10 days of life. This rate of excretion with an average dietary intake of 3.4 gm. a day would have allowed a retention of approximately 30 gm., less a negligible loss of about 0.3 gm. a day[17] in the feces. Although it is probable that in the last few days the dietary intake of potassium was less than that in the average diet, the significance of the disturbance in balance remains evident.

Because of the similarity of the ECG records from this patient and those reported as resulting from experimental potassium intoxication in dogs, two samples of serum and one of urine were analyzed by the chlorplatinate method.[8]* Both serum specimens were collected with care in a dry syringe. The first was centrifuged immediately; the second after standing for a few hours at room temperature. Examined spectroscopically, both were free of hemoglobin. The urine was a sample from the 425 cc. excreted in the last 2 days of life.

Although the normal level of serum potassium is between 4 and 5 m.eq./l., in this patient it was 8.85 20 hours before death and 10.5 a few moments after death. This is an elevation capable of causing cardiac arrest in dogs.[31]

The ECG changes could not be attributed to the small foci in the microscopic sections of the myocardium. Myocardial lesions similar to these have been described in uremia and demonstrated in the rare cases in which there was no widespread vascular disease.[7] However, neither with uremia[34] nor with myocarditis from other causes are there ECG changes comparable to those resulting from potassium intoxication.

The demonstration of fatal potassium poisoning in this patient, as

* The analyses were made by Dr. A. W. Winkler of the Department of Medicine, Yale University School of Medicine.

in experimental animals, is based on clinical rather than anatomic evidence. No structural changes have been observed at postmortem in animals experimentally poisoned with potassium, and except for the dilatation of the heart, none of the pathologic findings in this patient should be attributed to the action of potassium.

CASE 2. Med. rec. No. 20525. *Oliguria and azotemia, the characteristic ECG changes of potassium poisoning, and a terminal flaccid quadriplegia, following the therapeutic administration of large quantities of potassium salts.*

M. H., a single, 50 year old, white chauffeur entered the Peter Bent Brigham Hospital on February 15, 1923, complaining of inability to pass urine. He had used alcohol for years. Previous illness was denied.

Six days before admission, after 3 or 4 drinks of home brew, he appeared so "wild and unnatural" that a doctor was called, but no actual delirium tremens developed. He worked and felt well the following day and that night had another drink. The next morning he complained to his physician that he had passed no urine for 4 days. The administration of a proprietary diuretic and magnesium citrate had no effect. On the day before admission, after 5 days of anuria, catheterization yielded only a few drops of urine.

Physical Examination. He was a well nourished male who appeared comfortable and alert. Both the breath and the skin had a uriniferous odor. The skin appeared pasty, and there was a moderate edema of the lids and conjunctivæ. The optic fundi were normal. About the mouth there was a slight tremor during speech. The examination of the heart and lungs was not remarkable. The blood pressure was 175 98. The pulse rate was regular at 80 per minute. The abdomen was distended and diffusely tender. In the extremities the musculature was normal and the reflexes were described in detail as equal and active. There was no peripheral edema, and his general condition was good.

Laboratory Data. The erythrocyte count was 4,000,000 and the hemoglobin was read as 100% (Sahli). The leukocyte count was 9600, with a normal differential. The blood urea nitrogen rose from 105 mg. per 100 cc. on admission to 128 at death, while the blood creatinin increased from 17.1 mg. per 100 cc. to 19.1. The carbon dioxide-combining power of the plasma remained at 60 vol. %.

Four urine specimens were pale and cloudy, with specific gravities from 1.008 to 1.010. They contained a moderate amount of albumin and numerous red cells, white cells and casts. A stool on the 3d day contained mucus, but no occult blood.

Twenty-four hour urine specimens were analyzed quantitatively on the 5 days before death. There was a progressive increase in urine volume from 55 cc. to 1 liter per day, associated with an increase in the total excretion of urea and total nitrogen, titratable acid, creatin and creatinin. However, the amounts excreted were never more than a small fraction of the normal minimal values for these substances. No potassium determinations were made on the blood or urine.

Hospital Course. The patient felt and appeared fairly well for 5 days but on the 6th day developed a flaccid quadriplegia and died. During his hospital stay he continued to have abdominal distention, puffiness about the face and a uriniferous odor. He remained afebrile. The blood pressure, pulse and respiration did not change appreciably. As the daily urine output increased his weight declined from 75 to 71 kg.

Because of the anuria he was given a course of therapy routinely used for mercury poisoning, apparently for diuretic effect as well as for the purpose of preventing acidosis. This was called the Lambert treatment and included the administration of almost 2 gm. of potassium bitartrate in 250 cc. of water every 2 hours. It also included the periodic administration of 4 gm. of potas-

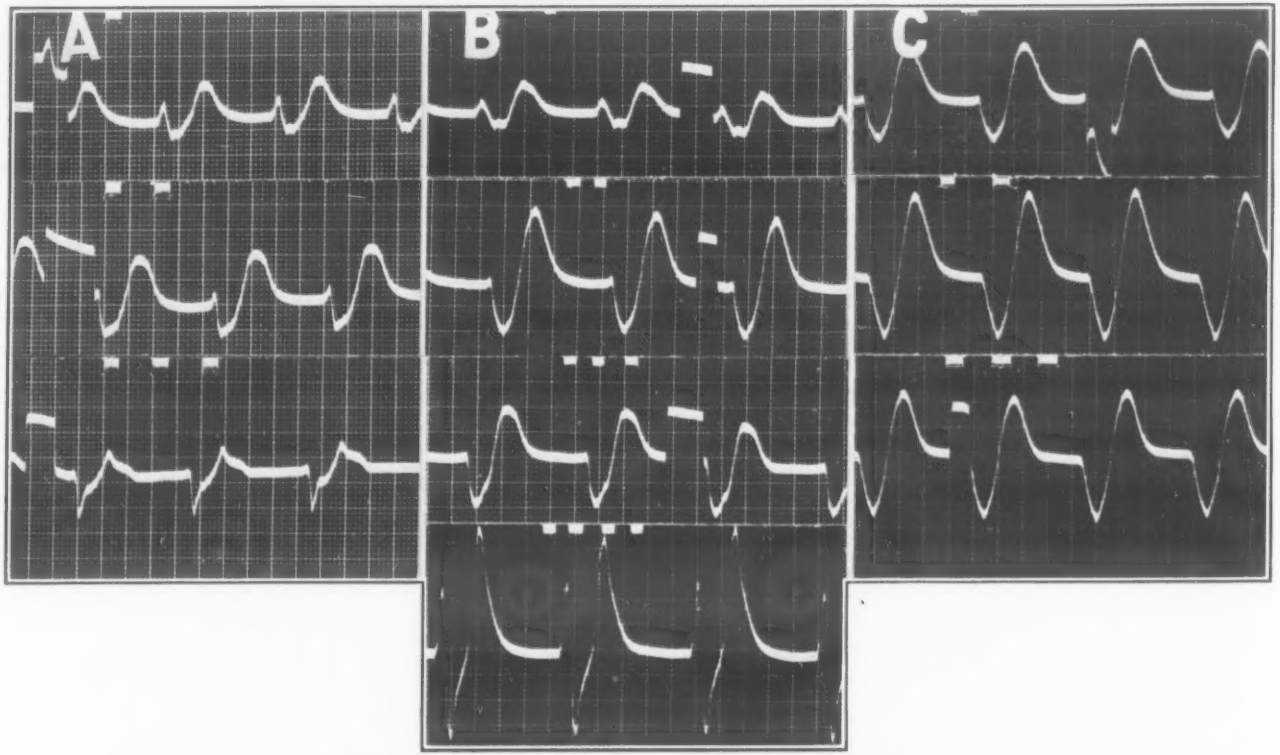

FIG. I.—AURICULAR ARREST AND IMPAIRED CONDUCTION*

A, Case I, Leads I, II and III, 24 hours before death and 4 hours after the onset of paralysis. Rate: 63 per minute P waves absent. Widespread intraventricular block. QRST: 0.6 second. Elevated T waves. *B*, Leads I, II, III and IVF, 5 hours before death. Rate: 59 per minute. Further elevation of T wave. Increased voltage. *C*, Leads I, II and III, 30 minutes before death. Rate: 65 per minute. The ventricular complex has become as mooth biphasic curve.

* Reproduced at ⅔ original size.

Widespread intraventricular block. QRST: 0.6 second. Elevated T waves. *B*, Leads I, II, III and IVF, 5 hours before death. Rate: 59 per minute. Further elevation of T wave. Increased voltage. *C*, Leads I, II and III, 30 minutes before death. Rate: 65 per minute. The ventricular complex has become as mooth biphasic curve.

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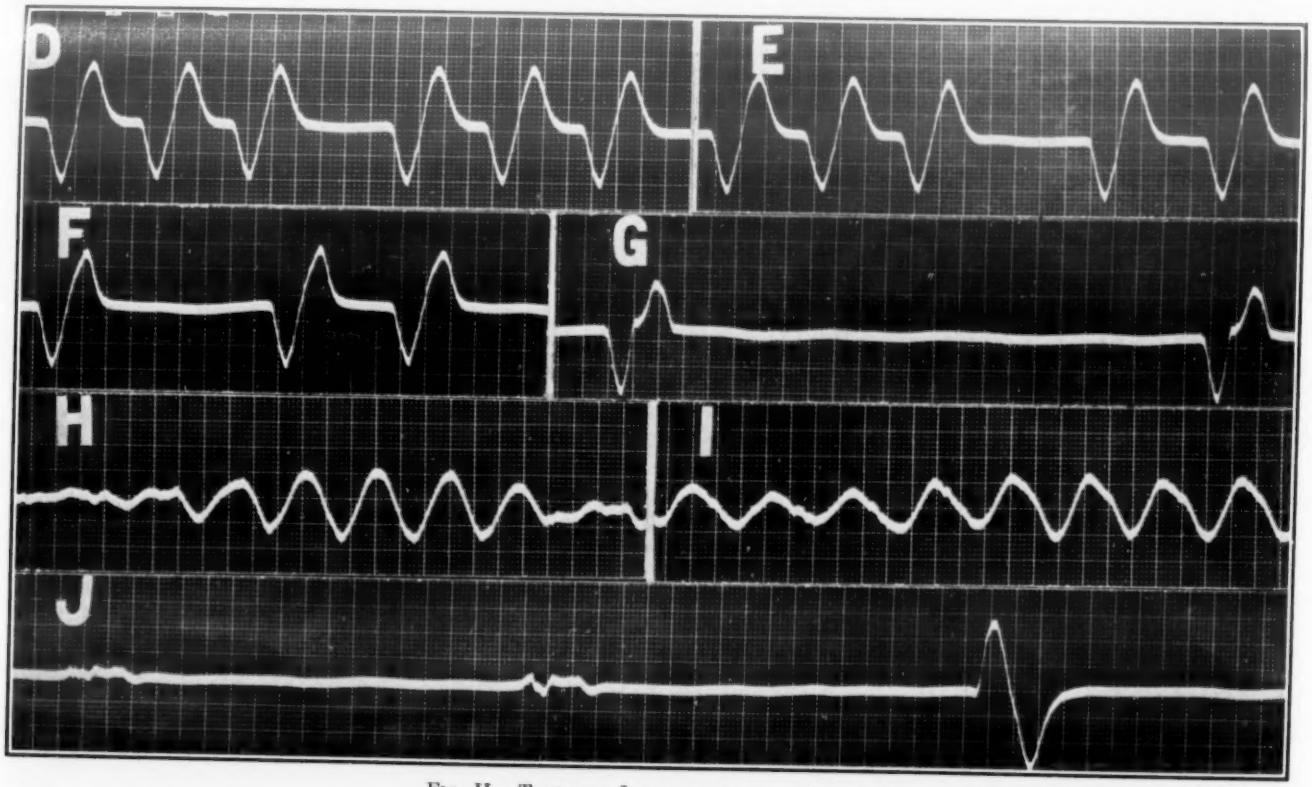

FIG. II.—TERMINAL IRREGULARITIES IN RHYTHM*

D, *E*, *F*, Ventricular complexes in groups of 3 and then groups of 2, at increasing intervals. *G*, Bradycardia. Rate: 14 per minute. *H*, *I*, *J*, Transient intervals of slow ventricular fibrillation followed by resumption of single varying abnormal complexes at irregular intervals.

* Reproduced at ⅔ original size.

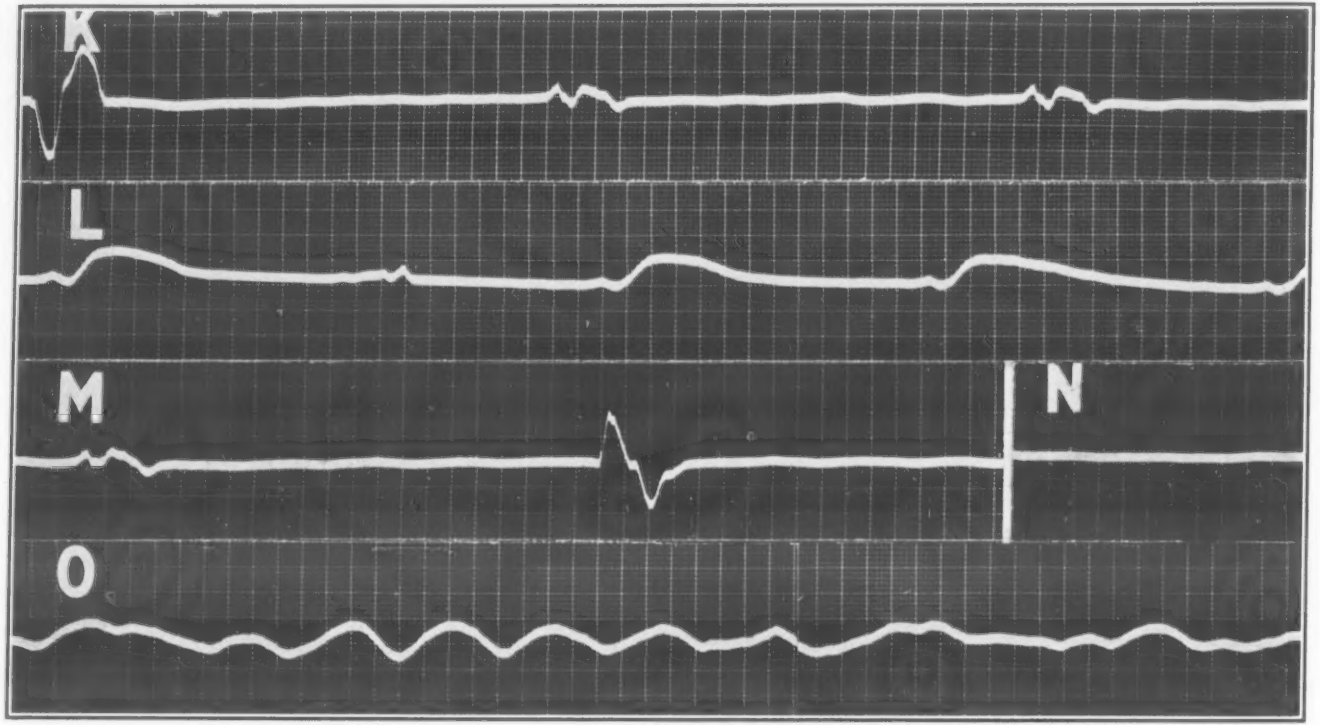

FIG. III.—CARDIAC ARREST*

K, *L*, *M*, Irregular ventricular complexes arising from various ectopic foci. *N*, Arrest of the heart. *O*, Postmortem ventricular fibrillation after intracardiac injection of epinephrin.

* Reproduced at ⅔ original size.

sium acetate in 500 cc. of water, by Murphy drip, infused slowly per rectum. The potassium acetate was given once on the 2d hospital day, once every 4 hours on the 3d, and thereafter was reduced to 2 gm. in 500 cc. of water at 8 hour intervals. On this régime he continued to feel weak and suffered from recurrent nausea and vomiting.

On the morning of the 6th hospital day the patient complained of increasing weakness in the legs. At 10:30 A.M., 5 hours before death, he was unable to bend his knees and showed marked weakness of the arms. The respiration remained normal and his mental state was entirely clear. At 1:30 P.M. the pulse had slowed to 28 beats per minute. At 3:10 P.M. an ECG was taken which showed "extraordinary curves with defective intraventricular conduction, suggestive of cor mortuum" (Plate IV).

Immediately after this, while he was being placed on his side for a lumbar puncture, the pulse became very slow and irregular, with dropped beats, and then stopped. The respirations had remained normal, but ceased a few seconds later. The patient was rational and answered a question within 30 seconds of his death, which occurred at 3:25 P.M., 15 minutes after the ECG had been taken.

Autopsy. The postmortem examination was reported by Dr. G. B. Magrath, the medical examiner, as showing diffuse chronic and acute nephritis, dilatation of the heart and edema of the lungs and brain.

Discussion. This patient survived 5 days of anuria before entering the hospital. During the 6 days on potassium therapy, there was an increase in urine volume and evidence of a beginning return of renal function. However, this return of function was never sufficient to affect appreciably the progressive course of the azotemia. The total daily excretion of the substances studied remained so small that the renal failure even on the last day of life was still nearly complete. From the laboratory data and other features of the case it is now apparent that in spite of a beginning diuresis the intake of potassium salts exceeded his excretory capacity. The total amount administered included about 20 gm. of the bitartrate daily and 4 to 6 or more gm. a day of the citrate for the last 5 days of life.

The final sequence of events corresponded closely to that of the case previously described, but was more rapid. There was a transitory bradycardia 2 hours before death, but regular rhythm was maintained. There was no change in the blood pressure until the end. The ECG (Fig. IV) showed arrest of the auricles and widespread intraventricular block. Terminal irregularities of the pulse were observed, corresponding with those of the previous case immediately before cardiac arrest. In this instance, as in the first case and in the experimental animals, the heart beat ceased before the respirations and the heart stopped in diastole. Again it may be noted that the patient remained conscious and able to speak up to the moment of death. In this case the diagnosis of fatal potassium poisoning is established on the basis of the clinical course and the electrocardiogram.

The Electrocardiographic Diagnosis of Potassium Effect. The work of Winkler, Hoff and Smith has made possible an ECG diagnosis of potassium poisoning in man. They showed that in dogs a slow increase of the serum potassium from normal levels of 4 to 5 m.eq./l. to 14 or 16 was accompanied by a progressive elevation of the T waves, depression of the S–T segment, intraventricular block, loss of P waves, and finally

K. L., M., Irregular ventricular complexes following fibrillation after intracardiac injection of epinephrin.

* Reproduced at 3 original size.

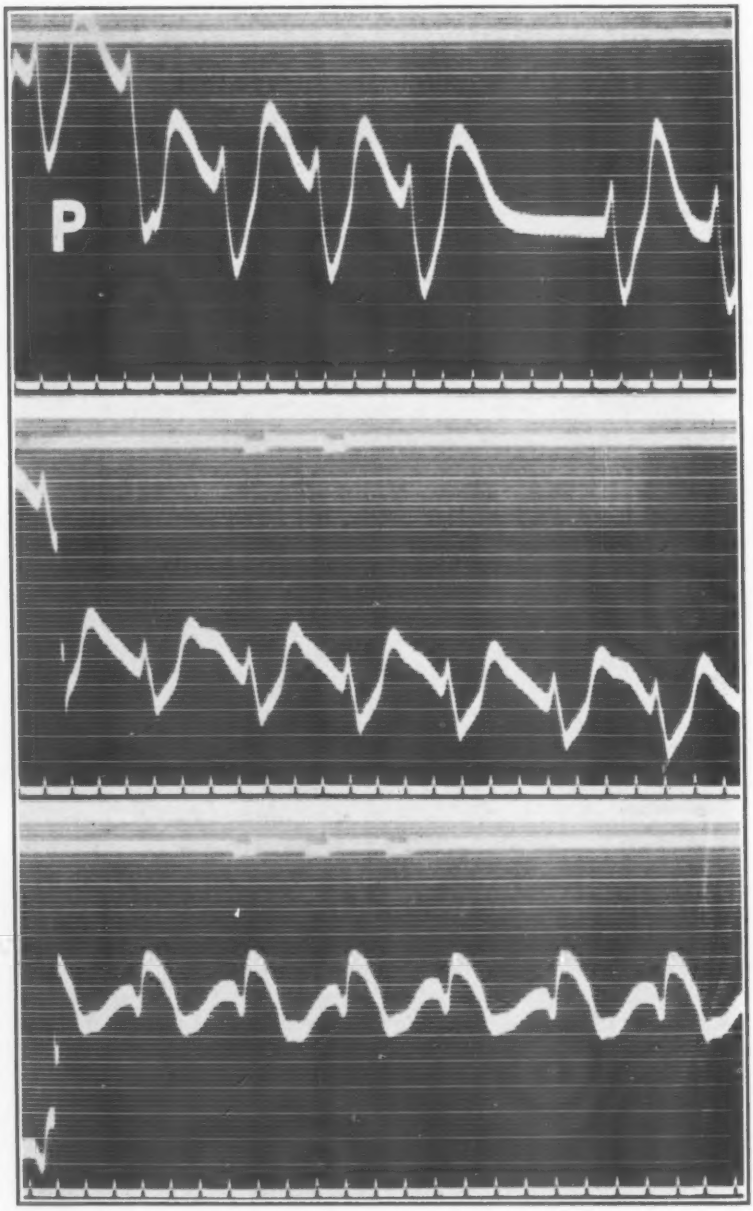

FIG. IV.*—AURICULAR ARREST AND IMPAIRED CONDUCTION†

Case II, Leads I, II and III, 15 minutes before death, and 4¾ hours after paralysis. Rate: 85 per minute. Absent P waves. Widespread intraventricular block. QRST: 0.75 second. The T waves are elevated and overlap each succeeding complex.

* Standardization deflection = 3 millivolts.
† Reproduced at ⅔ original size.

cardiac arrest. They also found that the ventricular fibrillation reported by earlier workers did not occur if the infusion of potassium salt was given slowly.[31] A rapid administration resulted in ventricular fibrillation.[15]

Subsequent studies demonstrated spontaneous potassium poisoning regularly in surgically anuric dogs[10] and occasionally in adrenalectomized dogs[32] as suggested by the work of Nicholson and Soffer.[16] Wood and Moe[33] found in heart-lung preparations from dogs that atrial and ventricular arrest occurred at average plasma potassium concentrations of 8.5 and 9.5 m.eq./l., respectively.

In man, the earlier effects of potassium on the heart have been described in the ECG of persons receiving potassium salts orally. These reports have shown elevations of the T waves[24] and in some cases an increase also in the P–R interval.[25] Two reports have also shown what now may be recognized as advanced toxic effects of potassium, including absent P waves and extensive intraventricular block. Each record was taken a short time before death. One of these was interpreted as showing a toxic effect resulting from the therapeutic administration of potassium salts, but no potassium determinations were made and cardiac arrest by potassium was not suggested.[21] The other, from a patient in uremia, was interpreted as due to a toxic depression of the Purkinje system, but the nature of the toxin was not specified.[29]

In the 2 cases described here the ECG changes observed in association with poisoning of the human heart by potassium were as follows:

The rhythm remained regular most of the time. The ventricular complexes increased in duration and developed progressively smoother and more rounded contours in contrast to the sharp QRS and T waves of the normal ECG. In Case 2 the successive complexes were so prolonged that they overlapped each other. In Case 1 the S–T segment was progressively depressed (Fig. I *A*, *B*) and then completely overlapped. The T waves became more rounded and markedly elevated. The sequence of changes preceding cardiac arrest in Case 1 included increasingly frequent and prolonged pauses in the rhythm, brief runs of slow ventricular fibrillation, and a series of variously deformed ventricular complexes. These changes were interpreted as indicating: (*a*) Suppression of auricular activity; (*b*) progressive slowing of conduction in the ventricles; (*c*) arrest of the heart associated with terminal irregularities of the rhythm and ectopic ventricular beats.

The absence of P waves results from arrest rather than from fibrillation of the auricles, as is shown by the persistence of regular rhythm. A degree of delay in conduction as great as that observed in these 2 cases is usually interpreted as representing bundle branch block. In these tracings, however, it represents an effect of potassium on the whole heart similar to that which occurs locally following direct topical application of potassium solutions to the mammalian heart.[27]

The runs of ventricular fibrillation which accompanied cardiac arrest in Case 1 correspond to the slow, reversible potassium fibrillation which occurs in association with dilatation of the heart.[13,28] The postmortem ventricular fibrillation recorded was a non-specific effect from

intracardiac epinephrin injection rather than an effect of potassium. The increased irritability of the heart due to epinephrin together with the slowing of conduction by potassium provided an ideal condition for the development of circus movements. Experimentally a rapid intravenous injection of potassium alone acts similarly.[15] The varying form of the terminal ventricular complexes represented varying sites of ectopic impulse formation in the ventricles.

The striking changes observed in the tracings from these patients provide a method for demonstrating physiologic effects of a quantitative disturbance in one of the plasma electrolytes. They also provide an etiologic explanation for certain bizarre terminal ECGs, formerly diagnosed non-specifically as *cor mortuum* or "dying heart."

Paralysis of the Extremities. In experimental potassium poisoning no paralysis has been observed. The animals die of cardiac arrest without accompanying evidence of paralysis. However, a functional depression of nervous tissue and skeletal muscle has been demonstrated following the topical application of 25 m.eq. of potassium chloride per liter.[3] In man, marked weakness of the extremities accompanied by paresthesia has followed an oral dose of 15 gm. of potassium chloride.[2] Paresthesias after comparable doses have been reported, accompanied by marked elevation of the T waves[25] and a somewhat lower serum potassium than that of Case 1.[12]

In the hours preceding cardiac arrest, paralysis was a striking feature in the course of each of the 2 patients described here. Since both were in uremia, substances other than potassium were also accumulating, although none of these are known to cause this type of paralysis.

The loss of motor power in each instance passed upward over the extremities in an ascending order. In the first case it lasted for 24 hours with an interval of partial remission. In the second it was present continuously for 5 hours. In each it was preceded by a sense of weakness and heaviness of the limbs, but by no other paresthesia or demonstrable impairment of sensory function. The musculature remained flaccid, and the tendon reflexes were absent. The head and trunk were not involved and there was no interference with respiration or micturition. There was no impairment of mental functions, although speech became thick just before death.

An apparent indication of a relationship of this condition to increased serum potassium is the fact that the subsiding paralysis in Case 1 returned after an oral dose of potassium chloride. Whether or not such was the case, the occurrence of sudden flaccid paralysis in association with high serum potassium suggests that it is important to differentiate such episodes from an attack of familial periodic paralysis.

The low serum potassium which occurs in familial periodic paralysis is associated with ECG changes unlike those described in these 2 cases. The changes in familial periodic paralysis include bradycardia, moderate block in conduction, and a characteristic flattening of the T waves.[22,23] These changes disappear after the injection of atropine,[23] while those from high potassium do not.[31] Moreover, once it is appre-

ciated that such an attack may occur in association with an elevation as well as with a diminution of the serum potassium, the differential diagnosis need present no difficulty, since high serum potassium is unlikely in the absence of advanced renal failure or anuria.

Effect of Renal Failure on the Serum Potassium. Normally the serum potassium level is controlled by the kidney, and any excess is promptly excreted. Even in the presence of somewhat impaired renal function, large oral doses have been tolerated. Chronic nephritics have received diuretic doses of 25 gm. of potassium chloride daily[5] and nephrotics, 12 gm. of the citrate and 12 of the bicarbonate daily.[9] Large quantities are routinely used in a variety of other conditions. Although as much as 48 gm. of potassium chloride a day have been given,[14] not more than 10 gm. are well tolerated in a single dose. Larger amounts are followed by elevated serum levels, cardiac effects, paresthesias, and an apparent temporary depression of renal clearances.[12]

Even in the advanced stages of chronic renal disease the renal excretion of potassium is sufficient to prevent the accumulation of a high blood level.[11,18] Toxic effects of potassium have been repeatedly suspected, but in the cases of evident poisoning the symptoms described were almost entirely those from a local irritating effect.[6] Early investigations of the serum potassium in severe nephritis and after experimental nephrectomy have, however, indicated elevated serum levels in a few instances.[10]

Recent studies have thrown new light on the relation of renal failure to potassium intoxication. It has been found that the survival time of anuric rats was decreased by a meat diet, and that the most toxic element in this diet was its potassium content,[1,4] and that a fatal accumulation of potassium occurs in anuric animals even if no food is given.[10]

As would be anticipated from this work, the potassium poisoning in the cases described here was made possible by a nearly complete failure of renal excretion.

Summary. Two cases of fatal potassium poisoning have been described. In one there was a spontaneous accumulation of the serum potassium to 8.85 m.eq./l. and a further elevation to 10.50 after an oral dose of 4.5 gm. of the chloride. The other had been given large therapeutic doses for 5 days. In each there was a failure of renal excretion.

The diagnosis was made by comparison of the findings in these cases with those reported in experimental potassium poisoning, including the serum and urine potassium levels (Case 1), the ECG, and the clinical course. The relationship of paralysis and of renal failure to potassium poisoning was discussed, and the ECG changes leading to arrest of the heart have been shown and described.

The parallel features of these 2 cases illustrating the clinical course of human potassium poisoning were the result of the combined effect of the potassium poisoning and the underlying disease. In each there was: (*a*) An acute uremia with oliguria; (*b*) recurrent nausea and retching; (*c*) episodes of bradycardia unaccompanied by symptoms of

cardiac failure or changes in blood pressure; (*d*) a sudden ascending flaccid quadriplegia without paralysis of the trunk or disturbance of speech or mental functions; (*e*) electrocardiographic changes including elevated T waves, absent P waves, intraventricular block, and terminal irregularities of the rhythm; (*f*) arrest of the heart in diastole prior to the cessation of respiration.

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ADDENDUM

Since this report was submitted for publication a third case of fatal potassium intoxication has been encountered. The patient was a housewife of 24 who became anuric as a result of acute nephritis in a single remaining kidney. Flaccid quadriplegia was absent, but death was preceded by the typical sequence of ECG changes and an elevation of the serum potassium level to 10.10 m.eq./l. No potassium salts had been given as such. The case will be reported in detail in a later paper.

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PROGRESS
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DERMATOLOGY AND SYPHILOLOGY

UNDER THE CHARGE OF
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THE TREATMENT OF EARLY AND LATENT SYPHILIS

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THE best approach to the modern treatment of early syphilis is a series of short, and to some extent disputable statements indicating landmarks in the progress of the past 35 years. This summary is substituted for the narrative type of historical perspective in this review.

The Mercurial Era. Syphilis therapy up to 1912 left the disease to pursue its physiopathologic course comparatively little influenced at least by the milder and hence most popular forms of medication—the therapy *per os* of the widely copied French school. Even mercury intramuscularly except as the water-soluble salts, and the violently reaction-producing calomel veneered the surface of a syphilitic infection rather than attacked its roots.

The Early Arsphenamine Era. The "therapia sterilisans" period or 1-dose cure era promised by Ehrlich's theorization slowly changed under the impact of criticism from older observers of the course of syphilis under treatment. The belief that something radical, time-saving and treatment-shortening had been accomplished by "606" died hard. One dose was succeeded by successive doses as experience grew. Relatively new conceptions of "cure by stage" came into existence with curious incomprehensible offshoots such as the doctrine of chancre-excision. "Abortive cure," essentially the systematic speculative underestimation of the amount of treatment required by the seronegative primary stage, dates back to this era. From 1916 to 1919 the "course" conceptions of syphilis treatment established themselves, together with a combined theoretical and speculative discussion of the necessity for and the appropriate use of arsphenamine and heavy metal.

The Early Evaluative Period. From 1919 to 1922, an extensive literature, unfortunately not too familiar to some claimants for priorities, constituted the initial "shake-down" of an accumulating experiential tradi-

tion. While limited to the serologic effects of treatment and the occurrence of grossly visible forms of relapse as criteria for determining effects, many of the outlines along which the new era has developed were foreshadowed by the reports of Gennerich,[17] the German Dermatological Society (Rost, 1921,[40] Almkvist,[1] Bering,[4] Boas,[7] Hoffmann,[21] Bruck,[9] Jadassohn,[24] Ullmann,[47] Eicke,[15] Hoffmann-Mergelsberg,[22] Müllern-Aspegren,[33] Haxthausen,[20] Rasch,[38] Scholtz[Silberstein[42]], Satke,[41] Mutschler,[34] Zieler,[50] Bruns,[10] Riecke,[39] Bernard,[5] Harrison[19] and others). The stage-of-beginning treatment conception received more or less precise delineation towards the latter part of 1922. A type of foreshortened intensified therapy, that of Scholtz, was reported by Silberstein[42] in 1923, before any American contributions were in the field. When American studies did appear, however, they rapidly established a series of important conceptions, beginning with Moore and Kemp's[31] demonstration based on Keidel's[30] foresighted Johns Hopkins system, of the importance of continuity in treatment, and S. W. Becker's[2] demonstration at the Mayo Clinic of the value of massing or intensification of arsenical therapy at the moment treatment is begun. Familiar to Americans during this period are the Pollitzer-Ormsby[35,37] variation on the Scholtz technic and other types of intermittent systems which lost ground after the League of Nations confirmation[28,46] of the substantial superiority of continuous treatment.

The League of Nations Syphilis Commission Evaluations.* Begun on a massive scale in 1928 with conclusions and recommendations stated in 1935, this world-wide survey of technical methods in the treatment of early syphilis provides the basis for what may now be spoken of as the conservative or prolonged method for the treatment of early and latent syphilis. Under the terms of the coöperative agreement among the nations participating, each was individually encouraged to make the most of his own material in addition to contributing to the general pool. This rapidly brought American material into the foreground, and the contributions of the Cooperative Clinical Group[13] working under the ægis and with the statistical coöperation of the United States Public Health Service, express today what might be called the basic formula of American practice. From the League of Nations evaluation for which Martenstein supervised the interpretations,[28] two general systems of treating early syphilis emerged —the British-Scandinavian intermittent and the American continuous systems. A certain amount of argument has inevitably arisen over the suitability of the material for deciding the question of intermittence *versus* continuity, but on the whole the Commission's findings seemed to justify the belief that the intermittence of the recommended intermittent system is more formal than actual and that its intensity especially in simultaneous arsenical and heavy metal administration, causes its effects to be substantially those of a somewhat less intensive but continuous technic. Enthusiasm for the newer foreshortened procedures (see below) should not be allowed to dim the significance of this great evaluative accomplishment, and the syphilologist of today may without hesitation subscribe to either of the announced conservative systems as the equal in curative

* Under the direction of the League of Nations Health Organization, the following countries participated: Denmark, France, Germany, Great Britain, United States of America. The membership in 1928 included Jadassohn (Breslau), Chairman, Madsen (Copenhagen), Colonel Harrison (London), Queyrat (Paris), Stokes (Philadelphia), Rasch (Copenhagen); Gougerot replaced Queyrat, Lomholt replaced Rasch in 1935. Statistical consultant, Westergaard (Copenhagen). Evaluation and report by Martenstein (Dresden).

effect of the more recent "hurry-up" systems of procedure with a substantially greater margin of safety.

Since the League of Nations evaluation has established such substantial landmarks, it may well be used as a milestone at which to summarize the high points of the progress of syphilotherapy since the close of the mercurial age. The following fundamental principles have emerged from a quarter century of revolutionary progress:

1. *Early and not late syphilis is the domain of systems.* Bad effects follow haphazardness, short courses, low dosage and lapse from treatment in early syphilis.

2. The "*stage at which treatment is begun*" *principle* is established with trustworthy evidence that seronegative primary syphilis is the most easily cured of all stages of the disease, seropositive primary syphilis the most uncertain or resistant and secondary syphilis midway between the two.

3. *Relapse follows short treatment*, especially arsenical, producing delayed secondaries, neurorecurrence, infectious mucosal lesions, serologic relapse and fastness.

4. *Single drug treatment is inferior to combined treatment* and a heavy metal improves arsenical results and compensates shortcomings.

5. *Prolongation*—more injections, longer courses—gives superior results in systems dominated by the calendar interval of 1 week. Prolongation and increased mass through individual and total dosage were, of course, attempts to meet the resistance of the 30% relapsing group among early syphilitics at large.

6. *Dosage theory* was spotted with empiricism. The concept of lower drug tolerance of the female as compared with the male; the large *versus* small dose school; the crowding or time-dose problems represented by the so-called intensive method; the toxicity fears (simultaneous *versus* alternate administration of arsenical and heavy metal); the idiosyncrasy and technical error factors in reaction interpretation which held down dosage, while reports of relapse and resistance raised it.

7. *Calendar servitude* or the domination of the 7-day interval on a purely empirical unevaluated basis was general. Few ventured to think in terms of shorter intervals or would admit their practicality or desirability.

8. *Rising appreciation of scheduling.* It became clear that schedules or systems critically examined by large syphilologic centers and expert experience were the sound basis for treatment methods rather than the results of blood serologic tests, thus slowly displacing the serologism of the 1920's.

9. *The vital comprehension of toxicity and therapeutic efficiency relations* was dominated by the laboratory and rested on the insecure foundation of trypanosomiasis in mice rather than syphilis in man or animals. This group of conceptions, though expressed by impressive numerical indices was essentially vague and inadequate. A true experimental basis for syphilotherapeusis did not yet exist.

10. *Despite these strictures on the knowledge of the day*, the work of individual investigators plus the League of Nations evaluations established the following facts:

(*a*) *An arsphenamine alone can "cure" early syphilis* in a large percentage of cases.[27]

(*b*) *Heavy metal is a potent augmenting force*, particularly true of bismuth; a fact recently "re-discovered" by recent workers with intensive methods.

(*c*) *Arsenical therapy can be "crowded"* or "foreshortened" without fatal effect and with good results (Scholtz-Silberstein massive divided dose system).

(*d*) *Continuity and calendar regularity* are vitally important to the conservative or prolonged systems evaluated by the League of Nations. "A little treatment continuously given is twice as effective as the same amount of treatment intermittently given."

(*e*) *Prolongation of treatment* (in the weekly calendar or conservative systems) irons out most complications, relapse and resistance.[3]

(*f*) *Some important League of Nations and Cooperative Clinical Group principles:*

(1) The curative outlook is one-third better when treatment is begun in the seronegative primary stage than in other stages of early and and latent syphilis.

(2) The good results obtained by prolonging continuous treatment longer than 1 year more than double those obtained by the same kind of treatment carried through less than a year.

(3) Intermittent and irregular treatment are the principal sources of delayed reversal of the blood serologic reaction.

(4) Prolongation and intensification of treatment, using much arsphenamine and heavy metal, but especially much arsphenamine in the first 3 months promotes good results.

(5) Satisfactory results may occur with little treatment, but much treatment and over prolonged periods is twice as effective as little treatment if continuously applied, and 5 times as effective as treatment intermittently applied.

(6) Arsphenamine is the chief factor in relapse prevention, and this applies specifically to the incidence of neurosyphilis (note importance of this principle in foreshortened intensive methods).

(7) Serologic irreversibility becomes the more marked the later in early syphilis treatment is begun, and the more frequently lapse from continuity occurs whether in the form of rest intervals or otherwise.

(8) A weak positive serologic reaction interrupting a series of negatives in early syphilis is a distinct warning of the possibility of relapse.

Much of the effectiveness of the foreshortened intensive treatment methods was predicted by Martenstein's conclusions from the general League of Nations material that the employment of a comparatively heavy individual dosage of the arsenical and of bismuth or mercury with administration in rapid succession at the outset of treatment, leads to superior results. Furthermore, approximately the same amount of treatment should be administered to primary as to secondary cases.

(*g*) *Large dosage is preferable to small;* should follow a weight standard, and be without sex differentiation.

(*h*) *Many of the most serious complications of treatment* are due to background causes (idiosyncratic-allergic, intercurrent infections, and technical factors rather than the drugs as such alone). In particular, the combination of arsenic and bismuth is as safe as arsenic alone.

(*i*) *To date, no claims for the use of a heavy metal alone* in the treatment of early syphilis have withstood critical evaluation. An arsenical is essential as a controller of infectiousness. The effect is augmented by bismuth, and also though probably less so, by mercury. Twenty full doses each of arsenical and heavy metal approximate a minimal amount of treatment for infection control (so-called 20–20 standard).

(*j*) *The controversies over the individual merits of arsenicals* (606, 914 and so forth) have been largely submerged by the overwhelming popularity of

mapharsen in American practice, due largely to its low toxicity, combined with high spirillicidal value. This has been overwhelmingly demonstrated in the 5-day massive dose arsenotherapy (5-day drip) and its therapeutic efficacy when intensively employed has also been demonstrated by the Eagle-Hogan animal experiments.

Additional Basic Principles for Present and Future Emphasis. 1. The Boeck[11] material underlies the principle that *syphilis "cures" itself* in 40% of cases.

2. A little treatment in early syphilis[36] raises the percentage of cure another 20% to 30%.

3. *Intensification and prolongation* (or repetition in the case of intensive foreshortened methods) directed at the resistant 30% bags another 15% to 25%, depending on stage-of-beginning-treatment, for cure.

4. *The remaining 5% to 15%* represents the irreducible residue of resistance (deficient defense, special strains and so forth) that nothing save time, therapeutic repetition and variation, and fever, if anything, will cure.

5. *Non-specific agents* (fever) have important re-enforcing and curative effects in early as well as late syphilis—chiefly by enhancing the effectiveness of arsenicals faster than it increases their toxicity.[6]

6. *The spinal fluid examination* is an indispensable evaluative and curative check procedure more important ultimately than blood serology.

7. *As to observation and discharge as cured*, all patients who have had an entirely non-relapsing course while receiving ideal treatment should be informed that a cardiovascular reëxamination in the 5- to 10-year period is necessary.

8. *The syphilitic pregnant woman* or the woman who has had syphilis and is believed to be cured should have her status reviewed with every pregnancy and safety-first requires her treatment for protection of the child during each pregnancy whether seronegative or seropositive.

9. *Unsatisfactory results* (non-cure) are usually reviewed by the 5th year of observation and Padget found no less satisfactory results in any case after 10 or more years of observation.

Principles Established by the Clinical and Experimental Study of Foreshortened Intensive Methods. The past decade of work with intensive treatment methods has contributed a number of additional important principles to our understanding of syphilotherapy.

1. Hyman and his co-workers[16] have demonstrated that an approximation to the *total curative dose of an arsenical can be administered to a human being* by an intravenous infusion method (drip) without necessarily disastrous effects with a controllable though increased toxicity and with satisfactory results.

2. *A toxicity-therapeutic efficacy relationship* has been worked out by Eagle and Hogan[14,16] on the basis of animal, and more recently human clinical results. Syphilis can be cured in 80% to 100% of cases (stage-of-beginning-treatment factor) by a total dose of 20 to 30 mg. per kilo body weight of an arsenoxide (mapharsen) alone.

3. *The toxicity of such a dose* is inversely proportional to the time in which this dose is given.

4. *Any combination of toxicity and time relationship* (that is, any margin of safety) that practical considerations may dictate is theoretically possible, the mortality rising with the shortening of the time in which the total dose is delivered.

5. *The addition of bismuth* ("re-discovery") *greatly enhances the effect* of

all foreshortened intensive arsenotherapy (informally estimated by Eagle as 8 times better effect with bismuth than without).

6. *Serologic signs and symptoms* under foreshortened procedure disappear gradually on a now well-recognized gradient to which a quantitative serologic procedure is essential in interpretation.

7. *A wide variety of time and technical variations* (5-day intravenous drip *versus* 10-day multiple injection, *versus* 10 to 12 weeks of 2 to 3 injections weekly, *versus* 26-week schedules) with graded morbidity and mortality but substantially identical therapeutic outcome can be employed as forms of "foreshortened intensive" systems in the name of various types of exigency or expediency.

8. *The mortality of the 5-day drip* is currently estimated at 1:200 to 1:300. Any schedule completed in 20 days or less will have a mortality greater than 1:1000 (Eagle-Hogan); 10- to 12-week systems have a mortality of approximately 1:1500. The mortality of 20- and 26-week systems is not yet definitely known. That of reasonably good performance of the standard conservative prolonged systems is estimated by Hahn[18] (Johns Hopkins Hospital) at 1:1950; with optimum experience at 1:2800. It must be recalled that the mortality of conservative treatment is computed from arsphenamine and not mapharsen-treated cases. The toxicity of mapharsen is so low (1 death in 3938 patients[16]), that a material drop in mortality should follow its use in the conservative systems. Levine and Keddie estimate the mapharsen death rate to be $\frac{1}{2}$ that from neoarsphenamine.

9. *The foreshortened intensive procedures* (up to 12 weeks) greatly reduce the incidence of neurosyphilis.

10. *The justification of the foreshortened procedures* except for their apparent efficacy in the prevention of neurosyphilis (spinal fluid abnormality) is in the main still one of emergency and expediency. The ultimate results are obtainable by the older slower methods with less risk of life. What effect this will have on their post-war use remains to be seen.

In a discussion of the basic principles of system evaluation applicable to foreshortened intensive methods, Stokes[43c] wrote as follows:

"Any new systems proposed should be judged basically by their ability (*a*) to equal or surpass the 'curative' expectancy of the old ones; (*b*) to lead to less infectious relapse; (*c*) to reduce the incidence of cardiovascular and neurosyphilis, and (*d*) by their relative risks to the patient.

"For the evaluation of a system, time and observation are necessary to establish reduction of, or absence of relapse and progression. For the former, 2 to 4 years; for the latter, up to 10 years is a reasonable observational requirement. For decision on relapse the patient must be repeatedly and frequently observed, for it is a come and go affair. For the evaluation of 'cure,' from a decade to a lifetime, the longer the better, is required.

"A system which under such scrutiny has shown itself at least equal to its predecessors may then proceed to claim additional advantage and support for a variety of reasons, including cheapness, rapidity, controllability of the lapse factor because the whole job is finished in a short time, aid in the widening of availability of treatment by making possible the treatment of more persons per unit of time, personnel and equipment. Such considerations are in the main secondary to those of control of infectiousness and real curative power.

"If the new system equals the old or surpasses it in all these particulars it has but one more hurdle to make before achieving priority. While

primum non nocere is losing some of its meaning in a war-torn world, there are still arch conservatives who are inclined to examine critically the bad effects, the complications of a system. Of real importance to the victim are the risks involved, the chances of damage or of death from treatment in the case of a disease which with none or very little treatment gives the victim at the outset a 40 to 70% chance of escape from serious consequences. If an equal chance of escape with an older method offering less risk exists, only the most cogent reasons and a free choice by the patient of the more dangerous method justify its election."

The Conservative or Prolonged Standards of Treatment for Early, Early Latent and Late Latent Syphilis. It is now in order to summarize what may be called the "official" or most widely authenticated and accepted systems for use in that phase of the disease which permits of systematization in procedure. While it is impossible, with the rapid changes taking place in syphilotherapy, to predict how long such systems will have a following, it should be clearly understood that they are effective, and will do all that the foreshortened systems will, with a very much greater margin of safety. To the British-Scandinavian intermittent system[8] (which must be exactly followed, diagram in hand) and a slight but now, for American practice, "official" modification of the American continuous (League of Nations) system, the "30–60–03,"[43] is added the as yet unproved and unevaluated but rational "Army Plan" recommended to the Surgeons General by the National Research Council and publicized in Circular Letter No. 74. The conservative systems are still, we believe, the backbone of modern practice, the basis of much of our present knowledge of mechanism and effects, and likely to be displaced completely only by certain radical changes in the whole chemotherapeutic attack on the disease such as are affecting the pyogenic infections, gonorrhea, etc. (the sulfonamides, penicillin).

The British-Scandinavian (League of Nations) System: Plan of Courses of Injection.

A course consists of 8 weekly injections of neoarsphenamine (0.6 to 0.75 gm. each) or arsphenamine (0.4 to 0.5 gm. each) given simultaneously with 8 weekly injections of an insoluble bismuth compound (0.2 to 0.24 gm. bismuth metal each) and followed by 2 more weekly injections of bismuth compound. An equivalent amount of a mercury preparation may be substituted for the bismuth (inunctions for 40 days at 3 gm. of unguentum hydrargyri or injections of 70 mg. of mild mercurous chloride or 120 mg. of mercuric salicylate, etc., suspended in a suitable base). It is recommended that:

(*a*) In cases which remain or become serologically negative during or by the end of the first course, 4 such courses be administered, with intervals of 3 to 5 weeks between any 2 courses.

(*b*) In cases which have not become seronegative by the end of the first course, in addition to the amount of treatment shown in (*a*), further courses should be administered until the patient has received as a minimum 3 beyond that which has ended with negative serum reactions. At the option of the individual clinician, this treatment may be prolonged as may be considered necessary.

(*c*) Cases presenting signs of clinical relapse of an early type should be dealt with on principles similar to those enunciated in (*b*).

For non-pregnant females, treatment should be administered on the plan outlined for men, with the exception that the single dose of neoarsphenamine should be reduced by 0.15 gm. and that of arsphenamine by 0.1 gm.

In the event of any reduction in the amount of treatment being indicated, it is recommended that this be effected by reducing the number of arsenical injections rather than by reducing the individual dose or increasing the intervals.

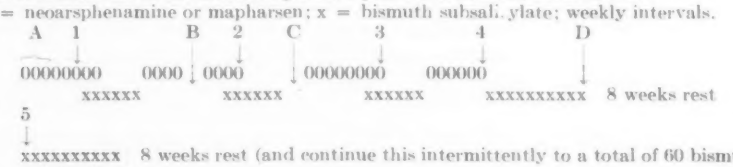
The American Continuous System: The "30–60–03" "Official" Modification, Circular Letter No. 18 of the Surgeon General's Office, U. S. Army. The published work of the United States Public Health Service and the Cooperative Clinical Group in the United States has indicated that continuous treatment with an effective arsenical alternating with bismuth on a definitely defined schedule with calendar regularity and without rest periods during the arsenical phase is the optimum conservative technic for the treatment of seronegative and seropositive primary syphilis, secondary syphilis, and early latency (within the first 4 years of the infection when the duration is known). An essentially similar standard of treatment employing 606, parallel with an acceptable intermittent (British-Scandinavian) system of treatment employing neoarsphenamine, has been recommended by the Commission on Syphilis and Cognate Subjects of the League of Nations as a result of an extended study of an international statistical material. It may therefore, it is believed, be accepted as having the support of authority.

For mnemonic convenience, the designation, "30–60–03" is suggested, for the standard system for early and early latent syphilis;[43] the "30" representing the number of arsenical injections; the "60" representing the number of weeks of bismuth therapy, equivalent to 60 injections of bismuth subsalicylate, and the "0" and "3" representing respectively, no rest periods, and 3 years of combined treatment observation. By "treatment observation" is meant the total elapsed time from the institution of treatment in accordance with this schedule until the patient is discharged from observation as presumptively cured.

Since the sequence of various types of treatment in this system, the prevention of relapse by overlapping of heavy metal and arsenical therapy, the serologic controls, the spinal fluid examination, all are integral parts of the treatment system, the following diagram is offered as presenting these various relationships.

The "30–60–03" for Early Syphilis.

30 neoarsphenamine or mapharsen injections, 60 weeks of bismuth injections.
NO rest intervals in the arsenical phase, 3 years of treatment observation.
0 = neoarsphenamine or mapharsen; x = bismuth subsalicylate; weekly intervals.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5
xxxxxxxxxx 8 weeks rest (and continue this intermittently to a total of 60 bismuth injections).

A = first 3 injections compressible into 10 to 14 days. Some risk of increased reactivity.
B = average case seronegative, 16th week.
C = Examine spinal fluid if blood is still positive, 24th week.
D = Always insist on spinal fluid examination before rest period.
1 = if blood test has become negative, suspect low resistance.
2, 3, 4, 5 = if weak positives appear among negatives, suspect relapse, neurosyphilis.

The "30–60–03" schedule as thus presented can be drawn up in "vertical" as distinguished from the above "horizontal" arrangement, week by week, for printing directly on record forms.

The published observation of the USPHS–CCG group on the treatment of early syphilis indicated that the "30–60–03" schedule could be most effectively applied to seronegative primary syphilis and fully developed secondary syphilis. In the case of seropositive primary syphilis, whose status should be confirmed in the seronegative cases by a repetition of the blood test on the day following the first

arsenical injection, there were definite indications that the seropositive primary phase of the disease, lacking the development of a full-fledged immunity reaction on the part of the body was the most resistant to cure, and the most prone to relapse of the 3 groups of cases included under the designation, "early syphilis." It has accordingly been proposed that in seropositive primary syphilis and initially negative primary syphilis which becomes seropositive on the blood immediately following the institution of treatment, a "40–80–04" system be employed, meaning thereby an additional 10 arsenical injections and 20 bismuth injections and another year of observation over and above the standards proposed as generally applicable to early and early latent syphilis. This extension of the arsenical phase of treatment can take the form of 5 courses of the arsenical of 8 injections each, in place of the 3 courses of 8 and 1 course of 6 injections in the "30–60–03" system. The bismuth therapy may follow the usual 2-injection overlap, plus 4 additional injections in the arsenical intermission that is employed in the "30–60–03"; the remaining bismuth injections to complete the 80-week standard, being continued in 10-injection intermittent courses after the completion of the arsenical phase of treatment.

The 26-Week Army System. The diagram is adapted from Circular Letter No. 74, Surgeon General's Office, U. S. Army.

Week	Arsenoxide	Week	Bismuth
2		1	
2		2	Bismuth subsalicylate intramuscularly once a week, 5 injections
3		3	
4	Arsenoxide intravenously twice a week; total 20 injections	4	
5		5	
6		6	Omit bismuth subsalicylate 5 weeks
7		7	
8		8	
9		9	
10		10	
11		11	
12		12	
13	Omit arsenoxide 6 weeks	13	Bismuth subsalicylate once a week, 6 injections
14		14	
15		15	
16		16	
17		17	
18		18	Omit bismuth subsalicylate 5 weeks
19		19	
20	Arsenoxide as in first course twice a week; total, 20 injections	20	
21		21	
22		22	
23		23	Bismuth subsalicylate once a week, 5 injections
24		24	
25		25	
26		26	

Dosage. Arsenoxide, 0.05 to 0.07 gm., based on patient's weight. Bismuth subsalicylate, 0.2 gm. (Forty injections arsenoxide—16 bismuth subsalicylate.)

Serologic Control of Treatment. In patients with early syphilis treated with the Army system, a serologic test will be done at the beginning and end of the schedule of treatment outlined but treatment may be stopped whether the serologic reaction for syphilis is positive or negative. After the completion of treatment the serologic tests should be repeated 3 and 6 months later. If the reaction is negative after 6 months, the case may be classified as "result satisfactory" and the *Syphilis Register* may be closed. If the test is positive after 6 months, the patient should be referred to a station or general hospital.

In patients with latent syphilis the serologic tests should be repeated at the completion of the treatment outlined, but the *Syphilis Register* may be closed when this treatment is completed, regardless of the result of the serologic test.

Spinal fluid examination should be performed in a hospital in patients with early syphilis at the end of the course of treatment outlined, or as soon as possible there-

after, but in any event before the *Syphilis Register* is closed. In apparent latent syphilis, spinal fluid examination should be performed in a hospital before treatment or as soon as possible thereafter, but in any event before the *Syphilis Register* is closed.

A System of Treatment for Latency—"24–60–100 plus." Before defining a system by which adequate treatment of latency may be judged, it must be reëmphasized here that the latency implied is "monosymptomatic seropositive latency" in which absolutely no clinical evidence of syphilis can be identified on complete physical examination except the positive and confirmed—and confirmable—blood-serologic reaction for the disease. An adequate examination of the spinal fluid is necessary to establish the fact that a seeming latency is not complicated by asymptomatic neurosyphilis. A patient who has been adequately treated for an early syphilitic infection but who still remains seropositive on the blood in order to be considered as in monosymptomatic seropositive latency (serologically fast) should have had a negative spinal fluid 1 year after the close of his treatment for early syphilis, and if more than a year has elapsed since the cessation of such treatment, a repetition of the spinal fluid examination is desirable. A long series of negative spinal fluids is not necessary to the establishment of the status of monosymptomatic seropositive latency, for according to USPHS–CCG observation, more than 1 or 2 repetitions of a negative fluid in the absence of any developing clinical signs is unnecessary.

The latency of a syphilitic infection is divided arbitrarily into an early and a late period, partly because of the greater risk of infectious relapse and other types of recurrence in early latency, and partly because of the presumed better outlook for complete arrest if not cure in the earlier years of the latent period. The dividing line between early and late latency has tended in American practice to be the fourth year of the disease. This is an arbitrary setting which may in the judgment of an expert, be varied one way or the other. A young and robust person whose infection is of 5 or even 6 years presumed duration may be advised to accept the standard for an early infection in his treatment. On the other hand most genuine latency, after the 4th year, shows relatively little tendency to progression, and may be treated by a standard substantially lower than that proposed for the radical cure of early infection.

The treatment of early latency (first 4 years of the disease) is that of early syphilis—the "30–60–03" system.

The Cooperative Clinical Group's[13] experience has indicated that for the treatment of late latency (after the 4th year) 3 courses of 8 injections each of an effective arsenical given in continuity and alternation with 10 injections of bismuth subsalicylate, without overlap and with continuity extending only through the arsenical phase, constitute an adequate beginning. The continuous treatment with arsenical and heavy metal is then followed by an intermittent and prolonged treatment with bismuth alone which should total, including the three 10-injection bismuth courses given with the arsenical phase, not less than 60 weeks of bismuth therapy. Further treatment with bismuth to the extent of 80 weeks, or even 100 weeks, or on the basis of 80 weeks, plus "a course a year" for several years, was found to increase appreciably the good results by the criteria employed. It is not necessary, however, in judging candidates for admission to the services, to insist on prolongation of the heavy metal phase beyond the 60th week. Approximately 70% of monosymptomatic seropositive latency may be expected to reverse to negative on the blood for an indefi-

nite period following a 24–60 course, and the failure of the remaining 30% to reverse may be regarded as no bar to eligibility.

As a general principle, late latent cases remaining seropositive after a 24–60 course should be observed at intervals of a year or two with physical examination and appropriate tests for evidence of cardiovascular progression and ultimate neurosyphilitic involvement.

It should be emphasized that late latency is usually much overtreated on the basis of fluctuating positive blood serologic reactions alone, or because of conflicts between the results of various laboratories ("serologic discord").

Massive Dose, Foreshortened Chemotherapy of Eealy Syphilis, Description of Procedure, Indications and Contraindications. All methods of intensive therapy are intended for patients with early syphilis (primary, secondary, relapsing secondary, and early latency) who have received little or no previous therapy, who are robust young people, especially men, reasonably free from serious visceral disease, particularly hepatitis, myocarditis, severe hypertension, nephritis, excessive alcoholism, blood dyscrasias, active pulmonary tuberculosis, and history of previous serious arsenical reaction. Although it is safe to administer sulfonamides simultaneously with conservative prolonged therapy and even with the 12-week system, it is unsafe to give sulfonamide therapy for gonorrhea or other conditions to patients receiving 5- to 10-day intensive therapy.

Pre-treatment Routine (*All Methods of Intensive Chemotherapy*) (after Leifer, 1940[16]). The routine examination consists of the following: 1. Daily urinalysis, including determination of urobilin.

2. Determination of the urea nitrogen content of the blood and the icterus index.

3. Complete blood count, including that of the platelets.

4. Complete physical examination on admission.

5. Serologic examinations made in 3 different laboratories (these include the Kolmer, Kline diagnostic, Kline exclusion, Kahn standard and titered Wassermann tests).

6. Dark-field examination of material from all open sores.

7. Estimation of renal function by determination of the specific gravity of the urine.

8. Special tests of hepatic function by the bilirubin method.

9. Studies of the excretion of arsenic in the urine and in the stool and its concentration in the blood (optional; for study purposes).

Technic of 5-Day Intravenous Drip (Chargin, Hyman, Leifer[16]) (after Committee on Massive Drip Intravenous Therapy, 1940). *Materials:* 1. Needle—deep injection type, No. 20, 1½ inch length.

2. Diluent—5% dextrose solution.

3. Drug—mapharsen (arsenoxide), ampoules 0.04, 0.06, and 0.06 gm.

4. Glass gravity cylinder, 300 cc. capacity with attached rubber tubing, glass drip chamber, adapter for needle. Vacoliter or similar container may be used instead of apparatus described (L. W. Shaffer).

5. Adhesive or Scotch tape (½ inch width).

Dosage of Mapharsen: 1. Total dosage for the 5-day treatment period is determined by the stripped weight of the patient. In patients weighing less than 70 kg. (155 pounds) the total dose is 1000 mg. (1 gm.); in those weighing 70 kg. or more, the total dose of mapharsen is 1200 mg. (1.2 gm.).

2. The daily dose is 200 mg. (0.2 gm.) for patients receiving a total of 1000 mg. (1 gm.).

3. The daily dose is 240 mg. (0.24 gm.) for patients receiving a total of 1200 mg. (1.2 gm.).

4. If a patient receives less than the intended daily dose (this will most often occur on the first day of therapy), the deficiency in dosage may then be spread over the remaining days of treatment. Thus, if the patient receives 120 mg. (0.12 gm.)

the first day instead of the intended total daily dosage of 240 mg. (0.24 gm.) he may be given 30 mg. (0.03 gm.) additional on each of the succeeding 4 days of treatment.

Procedure: Site of Election for Insertion of Needle. After cleansing of forearm and application of a tourniquet above the elbow to distend the veins, the needle is attached to a 2 cc. Luer type syringe and inserted in a vein on the forearm, usually anterior or outer aspect, between elbow and wrist, to allow movement at these articulations. Needle should be inserted into vein up to the hub, a gauze sponge placed beneath the needle hub, and the needle fixed in place with adhesive (or Scotch) tape. Alternate arms used on succeeding days.

The adapter of the intravenous set is attached to the needle (after the adapter has been freed of air bubbles) after the removal of the tourniquet, and the solution is allowed to flow rapidly until 10 to 15 cc. have entered. Should any swelling or infiltration be noted about the needle point, the flow should be stopped; the needle removed, and reintroduced into a different vein in the same or opposite forearm. The rate of flow is regulated by the fine adjustment clamp so that solution enters at a speed of about 50 to 60 drops per minute; thus, the entire quantity of 2000 cc. will require 8 to 12 hours for introduction.

Addition of Bismuth to Massive Dose Technic. Since July, 1941, L. W. Shaffer has been using bismuth concurrently with the arsenical. It may be used as follows:

Dosage of Bismuth With Intravenous Drip Method: 1. Suspension of bismuth subsalicylate in oil is employed.

2. The patient should receive 0.2 gm. bismuth subsalicylate (0.13 gm. bismuth metal) intramuscularly as soon as the diagnosis of early syphilis has been confirmed.

3. The second dose of 0.2 gm. should be given on the 3d day of treatment, the third dose of 0.2 gm. on the 6th day and a fourth dose of 0.2 gm. on the 9th day, before discharge.

Method of Preparing Arsenoxide Solutions. Mapharsen (arsenoxide), 0.01 gm., is dissolved in 100 cc. of 5% dextrose solution. Usual procedure is to prepare 500 cc. of such solution, containing 0.06 gm. mapharsen—this is enough for 3 hours of treatment.

When the Vacoliter containing 2000 cc. of 5% dextrose is used, the total daily dose of 0.24 gm. mapharsen (arsenoxide) is prepared the first thing in the morning and the solution allowed to run in, in the 10 to 12 hour treatment period.

This has been the practice in one institution. The preparation of the drug for the 10 to 12 hour period all at once has simplified the technic to a great extent.

Variants in Usual Procedure: 1. Primary fever on the 1st day (Herxheimer)—therapy is stopped if temperature reaches 101.4° F. or more. This usually happens between the 6th and 8th hour; by the time patient may only have received from 0.12 to 0.16 gm. mapharsen. The practice has been to compensate for this insufficient dose in the following manner: 1st day—0.12 gm. mapharsen (arsenoxide); 2d day—0.28 gm. mapharsen (arsenoxide); 3d day—0.28 gm. mapharsen (arsenoxide); 4th day—0.28 gm. mapharsen (arsenoxide); 5th day—0.24 gm. mapharsen (arsenoxide).

2. Clinical jaundice—when this appears in the course of treatment, the procedure should be interrupted. It has only been seen once in all cases studied (Committee report).

General Medical Care During 5-Day Intravenous Drip. Routine soapsuds enema should be given the night before treatment is begun, to obviate the need for bedpan, and whenever thereafter indicated. According to Leifer's (1940) description: "The nursing problem during the period of treatment consists of the preparation of fresh solution for each patient at the end of 2 or 3 hours and the refilling of the gravity flask. Meals are served on the ordinary bed tray. Patients can feed themselves. They are also capable of handling the urinal but, naturally, must be assisted somewhat in the use of the bedpan. The latter disturbance may be prevented by having the patient evacuate or have an enema during the evening, when treatment has been discontinued.

"The patients are given a high calory diet, rich in starches and carbohydrates. The majority of the patients read, listen to the radio, or play cards during the day. In the evening, after discontinuance of therapy, they may get out of bed. They

suffer little or no discomfort. Many of them register a gain in weight of as much as 10 pounds (4.5 kg.). This gain in weight is not due to any appreciable edema but may be explained by the fact that most of these patients otherwise undernourished, are so well treated with regard to food and nursing care."

Technic of 10-Day Multiple Injection Intensive Therapy for Syphilis.[16] With this treatment system patients need not be confined to bed, but they should be treated in the hospital and observed for at least 2 days after the last injection of mapharsen (arsenoxide). Routine ward diet may be employed.

Two injections of mapharsen (arsenoxide) are given daily for a 10-day period. The injections are given in the morning and evening of each day, 10, or preferably, 12, hours apart. Schoch, however, has given single injections of 100 to 120 mg. daily as an ambulatory procedure. Dosage is governed roughly by weight. Patients weighing 50-70 kg. (110 to 154 pounds) should receive 0.05 gm. of mapharsen twice daily for 10 days. Patients weighing between 70 and 90 kg. (155 to 200 pounds) should receive 0.06 gm. of mapharsen twice daily for 10 days. The dosage may be increased to 0.070 gm. in each injection for patients weighing over 90 kg. (200 pounds). Each dose of mapharsen (arsenoxide) should be dissolved in from 8 to 10 cc. of distilled water. The *solution should be aerated* and *rapidly injected*, intravenously, promptly after preparation. In cases where solutions are made in bulk, individual doses should be given within at least a 2-hour period after preparation.

On the 1st, 4th, 8th and 12th days, 0.2 gm. of bismuth subsalicylate in oil should be injected deeply into alternate gluteal muscles.

Thomas and his associates of Bellevue Hospital combine fever therapy with the intensive multiple syringe technic (1941, 1943). The risk of serious cerebral accidents with this method increases with the amount of arsenoxide (mapharsen) given. The addition of fever does not prevent cerebral reactions but lessens their frequency by necessitating a lower dosage of arsenical.

Reactions from 5- to 10-Day Intensive Therapy and Their Management. Minor Reactions: 1. *Pain in the arm:* cold wet dressings, ice-bag, aspirin, codeine only if pain is severe.

2. *Mild headache:* aspirin or codeine usually gives prompt relief. If headache is severe, increasing and persistent, consider this as possible prodrome of toxic encephalopathy.

3. *Nausea and vomiting:* give only fluids by mouth, and sedation if necessary. If persistent, discontinue treatment temporarily. May give 5% or 10% dextrose solution alone intravenously.

4. *Primary fever:* sharp rise in temperature occurs on the 1st day of treatment especially with intravenous drip. It is usually almost normal by evening, and normal by the next day. If the temperature goes above 101.4° F. discontinue drip for the day. Next day, drip may be reinstituted, practically always without recurrence of fever; this early fever need not cause omission of the second dose when multiple syringe method is used. Primary fever is usually accompanied by a flare-up of the syphilitic lesions (Herxheimer reaction, therapeutic shock). Symptomatic treatment may be used if necessary.

5. *Secondary fever:* secondary rises of temperature in excess of 101° F. at any time after the first day of treatment are an indication for interrupting therapy because secondary fever is sometimes associated with a mild toxicoderma. Most often in the 5-day treatment the fever occurs on the last evening of therapy. Mapharsen should not be given again until the temperature is normal. If fever recurs when treatment is reinstituted, efforts at intensive therapy should be abandoned entirely.

If the patient has received at least a total of 800 mg. (0.8 gm.) of mapharsen (arsenoxide) before the appearance of fever, intensive arsenotherapy by any system should not be reinstituted. In this case all further arsenical

therapy may be omitted, but the patient should receive a total of at least 12 weekly intramuscular injections of bismuth subsalicylate before all treatment is stopped.

Symptomatic treatment for this reaction may be used, if necessary.

6. *Toxicoderma:* usually appears in the post-treatment period on the 7th day, and is often preceded by and accompanied with fever. The type is most commonly morbilliform, scarlatiniform, or urticarial, and there is no exfoliation. This is not arsenical exfoliative dermatitis, and is not a serious sensitizing reaction. The rash usually fades in 1½ to 4 days without therapy. Symptomatic treatment may be used, when indicated.

Since this reaction does not usually occur with the intravenous drip method until all treatment has been completed, it has no bearing on interruption of such treatment. When the 10-day multiple injection system is used, the occurrence of this "9th-day erythema" is an indication for interrupting treatment. This reaction may be associated (rarely) with toxic encephalopathy, and continued treatment may increase the risk.

7. *Renal damage:* usually insignificant, consisting of minor traces of albumin, occasional red and white blood cells. No treatment is needed.

Marked albuminuria or hematuria is a signal for discontinuing treatment.

8. *Peripheral neuritis:* rarely encountered, and only in the post-treatment period. Usually manifested only by subjective symptoms, most often paresthesias. Objective changes are rarely encountered, and only sensory in type, never motor. The process disappears spontaneously. This reaction was common in the cases treated early by the 5-day method, probably because of immobility of the arm and the use of a drug too toxic (neoarsphenamine) for such a method.

9. *Nitritoid reaction:* rarely observed with multiple injections or with the intravenous drip procedure, unless the rate of flow of the latter is inordinately fast (mapharsen [arsenoxide] is well known to produce this reaction only rarely).

10. *Precordial oppression* (Falk and Rattner, 1942; Prats, Veras and Haraszti, 1942): this occurs occasionally with 5-day treatment. Disconcerting but not frequent or serious.

Major Reactions: 1. *Severe headache:* especially towards the 4th or 5th day of treatment, the occurrence of severe, persistent and increasing headache not readily relieved by aspirin or codeine should be viewed as of possible serious import (prodrome of toxic encephalopathy). It is best to discontinue intensive therapy and after a rest interval from all arsenical therapy of at least 4 weeks (this rest period to be occupied with weekly bismuth injections) to place the patient on the standard or 26-week treatment schedule, the duration of which may be shortened to the extent of the mapharsen dosage before the reaction occurred (*e. g.*, if the patient received a total of 400 mg. mapharsen before the reaction, 1200 mg. additional should be given by injections twice weekly with bismuth added as in the standard schedule).

2. *Jaundice:* this is an uncommon complication and calls for discontinuance of intensive therapy. No instance of acute yellow atrophy has occurred although Rattner and Falk (1942) observed a case of severe hepatitis with other visceral damage (see below). For the treatment of this reaction, the patient may be given intravenous 10% dextrose solution, high carbohydrate-low fat diet, and injections of liver extract therapeutically. Intestinal elimination should be encouraged with saline catharsis.

3. *Blood dyscrasias* (especially purpura or bleeding from any part of the body): rarely encountered, but necessitating permanent discontinuance of all arsenotherapy. Treatment usually consists in blood transfusions.

4. *Exfoliative dermatitis:* rarely, if ever, encountered. Requires permanent discontinuance of all arsenotherapy. Symptomatic treatment, dextrose intravenously, and liver extract.

5. *Encephalopathy:* women are especially susceptible. This reaction may be manifested by severe headache, vertigo, tremor, fever, unusually severe nausea and vomiting, mental confusion, disorientation, and apathy; by single or repeated convulsive seizures, and by prolonged chorea. In serious instances hyperthermia usually supervenes and *death* may result. May occur on the 3th to 5th day of treatment, or not until the 6th or 7th day; rarely thereafter. Often preceded by headache of increasing severity (see above). There is no means of anticipating this reaction (Thomas, Wexler and Dattner, 1942). In mild cases, the suspicion of toxic encephalopathy should be checked by examination of the spinal fluid for cells, globulin or increased protein. If such tests are positive, further treatment with arsenical drugs should be abandoned. If the spinal fluid is normal, treatment may be resumed if the symptoms have completely disappeared and the temperature is normal.

Treatment of this serious reaction is of uncertain value but the prognosis is not as bad as is usually assumed (Chargin, 1940). Suggested procedures include (1) repeated drainage of spinal fluid (20 to 40 cc.) in repeated taps daily; (2) dehydration by use of intravenous 50% sucrose solution, 50 to 200 cc.; (3) sedation is of value in all cases. Where symptoms are mild, any of the barbiturates may be used by mouth. If convulsions occur, sodium amytal 0.24 gm. ($3\frac{3}{4}$ gr.) may be given intravenously or intramuscularly (this dose may be repeated every 2 to 3 hours for several doses if convulsions occur or the patient is restless; (4) adrenalin. Oxygen inhalations may also be given. Sodium thiosulfate is of no value (Chargin, 1940).

6. *Severe renal injury* (rare); Thomas and his colleagues (1943) have reported acute nephrosis in patients receiving short arsenical and prolonged fever treatment but no particular renal damage occurs in their patients treated with the multiple injection method (10- or 6-day). Rattner and Falk (1942) reported a severe case with acute glomerulonephritis, anuria, uremia, hepatitis, ileus and pericarditis in a patient treated by the 5-day method. This is *rare*.

Post-treatment Routine After 5 to 10 Day Intensive Therapy (to be carried out before discharge from hospital). (1) Complete physical examination. (2) Laboratory studies. (*a*) Titered blood serologic test for syphilis. (*b*) Complete urine analysis. (*c*) Complete blood count (hemoglobin, red blood cell and white blood cell count and differential). (*d*) Other laboratory procedures (icterus index, serum bilirubin, urobilinogen, non-protein nitrogen where indicated).

Outline of Proposed 12-Week Schedule of Modified Intensive Treatment (Eagle, 1943). Patients are to be treated with mapharsen (arsenoxide) 3 times weekly (Monday, Wednesday, and Friday; or Tuesday, Thursday, and Saturday) at the following dosage scale: less than 120 pounds (55 kg.), 50 mg.; 120 to 155 pounds (55 to 70 kg.), 60 mg.; greater than 155 pounds, 70 mg. Treatment is to continue for 12 weeks or to a total of 36 injections. Hospitalization is not necessary, and patients are to be treated on "duty status." Patients are to receive intramuscular injections of bismuth

subsalicylate (0.2 gm., equivalent to 0.13 gm. of metallic bismuth) once weekly throughout the course of mapharsen (arsenoxide) treatment, to a total of 12 injections.

Follow-up Observation After All Methods of Intensive Chemotherapy. 1. Patient should be reëxamined at monthly intervals for 6 months.

2. This reëxamination should include a complete physical examination with special attention to the mucous membranes of the mouth and throat, the genitals and the perianal region for easily overlooked evidences of infectious relapse.

3. Quantitative blood serologic tests for syphilis should be performed monthly for 6 months, and then at the 9th and 12th month. (The blood serologic reactions usually become negative at the 12th to 16th week after the start of treatment).

4. Examination of the spinal fluid should be done, if feasible, sometime between the 6th and 12th month.

5. The patient should not receive any further anti-syphilitic therapy, except as specifically set forth under "management of the unsatisfactory case."

Management of the Unsatisfactory Case. A patient who has become clinically "cured" and serologically negative and remained so until the 12th month of observation, and in whom the spinal fluid is negative, may be discharged from observation as a "satisfactory result." Should such a person return at a later date with a new dark-field positive lesion, this may be considered as a new infection and the patient may be re-treated in the original manner (Schoch, 1943; Moore, 1943; L. W. Shaffer, 1943). A case must be considered as unsatisfactory or a treatment failure, if: (*a*) There is definite objective evidence of infectious relapse, corroborated by a positive blood serologic reaction for syphilis, and if possible by positive dark-field examination. (*b*) There is incontrovertible evidence of serologic relapse without clinical relapse, *i. e.*, the patient's blood serologic reaction has dropped to negative or near negative and then to persistently strongly positive (this is best interpreted by a quantitative procedure). (*c*) Reagin fastness, *i. e.*, where the blood serologic reaction for syphilis has never reverted to negative but remains persistently positive (preferably determined by a constant titer of quantitative tests) for a 6 months period after treatment.

The unsatisfactory case (infectious relapse, serologic relapse, seroresistance, and the new infection) may be re-treated by intensive therapy except in the event of serious reaction from the original treatment. The results of intensive re-treatment of the unsatisfactory case have not been fully evaluated, but appear to be less satisfactory than original treatment.

Special Considerations Concerning Early Syphilis Treatment. *Criteria of Adequacy of Treatment for Syphilis.* The answer to this question depends fundamentally upon the definition of "adequacy." If by adequacy is meant the securing of a condition of non-infectiousness in an infectious case, one kind of answer will be appropriate; if adequacy is to be interpreted in terms of clinical or of radical cure, another answer will be appropriate; if adequacy means the placing of an infected individual at one or another type or stage of involvement in syphilis on asymptomatic status that will permit of full or limited service in the armed forces, still another answer is necessary. The subject is dealt with under each of these three heads briefly as follows:

Treatment of Non-infectiousness. The immediate infectiousness of surface lesions of syphilis is controlled in all but the rare treatment-resistant or arsenic-fast case, it will be recalled, by the first one, or at most two, injections of an effective trivalent arsenical, provided the dose is adequate (0.3 to 0.5 gm. arsphenamine 606; 0.4 to 0.6 gm. neoarsphenamine; 40 to 60 mg. mapharsen). The duration of this effect of 1 or 2 injections is not precisely known, but is estimated roughly as approximately 30 to 90 days. Failure to continue treatment does not necessarily, but may in a percentage of cases ranging from 0% to 64%, lead to infectious relapse.

A useful tabulation from the Cooperative Clinical Group and the University of Pennsylvania material is herewith presented:

Arsenical treatment alone, number of injections	Infectious relapse (%)	Additional heavy metal injections	Infectious relapse (%)
1–4	64	20†	45.0
5–9	14	20	9.0
10–19	..	20	4.0
20–29	..	20	3.6
28.8*	..	28.2 or more	0
30–40	..	"appropriate"	1.2

From this tabulation it will be apparent that the critical point at which sharp reduction in the probability of recurrent infectiousness takes place is between the 5th and 9th injections of the arsenical (14% relapse without and 9% with heavy metal); and that the so-called 20–20 standard, often quoted as adequate for treatment to non-infectiousness, reduces the risk of infectious relapse to 4%, beyond which a slow reduction to 0% to 1.2% is secured by prolonging treatment beyond 20 arsenical injections with 30 or more injections of heavy metal.

Heavy metal, in the statistical table presented above, is taken to represent 0.2 gm. of an insoluble bismuth salt of not less than 57% metallic content, or 1 week of mercurial inunctions, or its intramuscular equivalent in a water-soluble or insoluble mercurial salt.

It will presently be apparent therefore that the best treatment to secure non-infectiousness is practically identical with the optimum treatment for the securing of "satisfactory results" or "cure."

The Influence of the Development of Secondaries on Relapse. An interesting and seemingly paradoxical situation was revealed in the comparison of serological with clinical relapse under treatment—a relation of particular importance because it might well form the basis for polemic discussion. The stage of syphilis at which treatment is begun influences the incidence of mucocutaneous relapse in a different way from that in which it affects all other forms of relapse. The first Cooperative Clinical Group survey of mucocutaneous relapse as such[44] indicated that it occurs in 10% of patients beginning treatment in the seronegative primary stage; 8.6% of those beginning treatment in the seropositive primary stage; and only 4.2% in those who began treatment after their secondaries had fully developed.‡ Relapse incidence of the mucocutaneous type was therefore markedly less if the patient was allowed to develop his full cutaneous secondary reaction to the disease, the difference amounting to as much as 58% reduction in probability as the patient passed from a seronegative primary to the florid secondary phase. On the other hand, the existence of a distinct relapsing type was foreshadowed by the fact that patients who began treatment with late or recurrent secondaries relapsed in 22.3% of cases. Serologic relapse, on the other hand, occurred in 12% of patients whose treatment was begun in seronegative primary syphilis; 15.1% under the same circumstances in early secondary syphilis (1st year); and 20% if treatment was not begun until delayed secondaries after the 1st year. It appears, therefore, that to begin the treatment of a patient in the sero-

* University of Pennsylvania figures; all others are C. C. G.

† One week of mercurial inunctions equals 1 injection.

‡ The percentages estimated on the basis of 3244 cases observed and treated for six months or over were seronegative primary 16.4%, seropositive primary 20.2%, secondary (first year) 9.5%, secondary delayed 9.2%. The principle illustrated is the same in both.

negative stage of primary syphilis, while it has already been shown definitely to increase the prospect of complete cure, nonetheless subjects him to a definite slight risk of mucocutaneous recurrence and therefore of more prolonged infectiousness. The probable explanation, of course, is that the skin and mucous membranes have never been given the opportunity to develop what might be thought of as a local tissue immunity by full reaction to the disease.

It must, of course, be appreciated that the reduced incidence of relapse and progression in patients who have had secondaries arises simply from the fact that in reaching that stage they have automatically, so to speak, set behind them that much of the life history of the disease. It must, too, remain for further study to decide whether the increased risk of infectious recurrence after early treatment justifies postponement until the patient has developed secondaries. At the present time the higher proportion of curative results seems to justify immediate treatment rather than postponement. The increased risk of infectiousness through recurrence can hardly be greater than the risk of infectiousness represented by a patient who is allowed to live at large in the community without benefit of the arsphenamines until his secondary eruption has fully developed. In any event, the application of such a principle demands universal hospitalization for the patient between the primary stage and the full development of secondaries, an obvious impracticability at this time. Until the proponents of postponement (as for example, Bernard) can advance indubitable evidence that there is other than merely mucocutaneous protective value in permitting a patient to go on to secondaries, the postponement of treatment until secondaries develop is not only against the interests of the public health but against that of the individual patient who above all things, desires the greatest possibility of personal cure.

Jadassohn, from an international questionnaire,[24] has reported that the effect of arsphenamine in controlling the infectiousness of syphilis had led to an estimated reduction in incidence of new cases of the disease of 75% to 80% in Belgium, Sweden, and Holland; 60% in Finland; 50% in Denmark; 50% to 80% in Switzerland; 30% to 60% in Italy and Czechoslovakia; and 25% in Norway.

Rules for Preventing Infectious Relapse. The prevention of infectious recurrence and the reduction of relapse to the lowest possible terms requires of the practitioner, then, an unhesitating acceptance of the following rules: (1) The concept of abortive cure by short courses should be abandoned, no matter how early the patient may come under treatment. (2) Not less than 20 injections of an arsphenamine, and more if possible, preferably in 1 or 2 courses, and an equivalent amount of heavy metal without rest intervals, should be given in an early case to control infectiousness. (3) Treatment should be continuous rather than intermittent or intensive, there being no time, at least within the first year or more, that the patient is not under the influence of one or another effective mode of treatment for syphilis with an arsphenamine or heavy metal. (4) Treatment should be massed well to the fore—that is, within the first 3 months, for this is the period in which mass as distinguished from prolongation, reaches its greatest effectiveness in preventing relapse. (*Cf.* Massive dose arsenotherapy.)

Stokes, Miller and Beerman[45] in their study of bismuth arsphenamine sulfonate observed a similar phenomenon. The proportion of relapse in continuous treated cases was 9.1% and in those allowed rest intervals 14.3%. Of the continuously treated cases 60% had comparatively little treatment (20 injections or less) while

86% of the intermittently treated patients who had the higher incidence of relapse had had comparatively heavy courses of 21 injections or more (40% had over 40 injections). It appeared that a small amount of treatment continuously applied yielded fewer relapses of all kinds than a larger amount with rest periods or lapses.

With so much emphasis placed on the seriousness of lapse in the promotion of infectious recurrence, it is proper to emphasize as the 5th rule for the physician, his responsibility in educating his patient and in holding him to a sufficiently prolonged course and in utilizing follow-up assistance if and when it is available. (6) He should understand, too, that infectious relapse is detected by actual physical examination with special emphasis on the mouth, anus, and genitalia rather than by serologic tests. One should examine especially the lips, penis, scrotum and vulva. (7) Positive serologic tests may warn of infectious relapse and confirm the diagnosis, but since they cannot be frequently applied, physical examination and instruction of the patient himself in the recognition of infectious lesions are the more important approaches. (8) Serologic tests and stripped physical examinations, to be of value in detecting relapse, should, if anything, be more frequently made after treatment is completed and the patient is put on observation than during treatment itself. The opposite is common practice, and this applies especially to the first 2 or 3 years of the disease. (9) Negative serologic reactions, as has been repeatedly emphasized, are not proof of non-infectiousness, immediate or future. A negative serologic reaction should not deceive the physician or patient into relaxing precautions. (10) Treatment and time are the chief preventives of infectiousness. (11) Since potentially infectious relapses occur overwhelmingly in the first 2 years of early syphilis, sexual relations and intimate contact without absolute protection should be allowed *only while the patient is under actual arsenical treatment.* The duration of non-infectiousness when treatment is stopped before the 12th injection of arsphenamine may not, apparently, exceed 1 month.

Adequacy With Respect to "Cure" or "Satisfactory Results." Information on this subject is based on case material observed for not less than 2, and upward to 20, years since the onset of the infection or the institution of treatment. Material of less than 2 years of observational control is fundamentally weak in its demonstration of the possibility of relapse, since the first 2 years of infection are overwhelmingly those of relapse predisposition. On adequacy in the sense of "satisfactory results," 5 groups of data will be quoted: (*a*) Cooperative Clinical Group results in the treatment of early syphilis by a continuous alternating use of arsenical and heavy metal without rest period, through 65 weeks of treatment observation; (*b*) Padget's[36] Johns Hopkins Hospital Syphilis Clinic report on 551 patients completely reëxamined 5 years or more after the termination of their original treatment for early syphilis; (*c*) optimal treatment for early syphilis, 1 to 20 years observation;[12] (*d*) a shortened 20-week system, Hood[23] reporting on Johns Hopkins Hospital material; (*e*) the 5-day intensive intravenous drip arsenotherapy of syphilis (without the use of heavy metal), Leifer, Chargin and Hyman (1941) and Elliott, Baehr, Shaffer, Usher and Lough (1941).[16]

It is not possible at this time to offer more than speculative estimates on 10-day multiple syringe and 10- to 12-week intensive mapharsenbismuth[16] systems which are under study.

The Cooperative Clinical Group's standard treatment system experience indicates that for satisfactory results, treatment must be continuous and not inter-

mittent or irregular, and must combine the alternate use of an effective arsenical (mapharsen is not represented in this material) and a bismuth. Striking reductions in effectiveness with occurrence of infectious relapse, progression of syphilitic manifestations, serologic relapse and seroresistance occur in all phases of early syphilis in which intermittence or irregularity is allowed to occur. Disregarding the precise system of administration, the highest proportion of satisfactory results in seronegative primary syphilis was obtained with 10 to 19 injections of arsphenamine with accompanying heavy metal; in seropositive primary syphilis, with 25 to 35 injections; in early secondary syphilis (seen in the 1st year) 20 to 29 injections. Higher rather than lower dosage of the arsphenamine is recommended. Failure to secure a satisfactory result by 20 injections or less may be met by 10 additional injections, plus heavy metal, which may double the proportion of unsatisfactory outcomes reclaimed. The irreducible margin of failure in the treatment of early syphilis by older standards ranges from 4% to 27%, depending on method, stage at which treatment is begun, adequacy of treatment during the first 2 years of infection.

The Johns Hopkins Syphilis Clinic material[36] is particularly valuable because of the length of observation (over 10 years in half of the patients), and shows clearly the importance to adequacy of the treatment results of the stage at which treatment is begun (82% cure in seronegative primary syphilis, 68.8% in secondary syphilis, 58.7% in early latent syphilis). The poorest results, as in the Cooperative Clinical Group series were observed among patients whose treatment was begun in the seropositive primary stage. Cure was obtained by 83.4% of the patients whose treatment during the first 6 months was by a continuous system, and is increased to 90.4% if treatment during the next 6 months was likewise continuous. It was shown that the final or "adequate outcome" depended in a directly quantitative fashion not only on the number of doses of the arsphenamine received, but also inversely, upon the time span during which it was given. In other words, the more injections in the shorter time, the better the results. The development of early or intermediate relapse was found to be of grave prognostic significance.

Cannon found in a series of some 600 patients treated with 3 standard arsphenamines, that arsphenamine 606 was incontestably superior to neoarsphenamine or silver arsphenamine, and that 1 year of regular and continuous treatment with the arsenical injections closely spaced (2- and 3-day intervals in the first 3 to 5 weeks and at intervals of not less than 1 week thereafter) gave the highest proportion of satisfactory results. The difference between seronegative primary, seropositive primary and secondary syphilis was not more than 6%.

The 20–20 Arsenical-Bismuth Simultaneous Injection Course (Hood). This shortened system, not comparable because of longer intervals (weekly) with the 26-week system of Circular Letter No. 74, utilizes weekly injections of mapharsen and simultaneous weekly intramuscular injections of an oil-suspended bismuth salt. The maximum period of observation (33 months) was only sufficient to indicate that the proportion of unsatisfactory results in the form of seroresistance, serorelapse, clinical relapse and involvement of the central nervous system, amounting to 13.6% of the observed series, was approximately that of unsatisfactory results obtained in early syphilis treated with other arsenical drugs and treatment systems. If confirmed by longer observation, such a treatment system should show how little rather than how much treatment is necessary to produce the average or so-called "standard" results which are so strikingly uniform throughout the entire range from 5-day intravenous drip to 65-week continuous combined therapy.

Massive Dose Arsenotherapy ("*5-Day Drip*"). The 2 series, Leifer *et al.*, and Elliott *et al.*, the former with of course the longer series of observed cases, illustrates the following principles regarding adequacy: (*a*) Curative results can be obtained with a trivalent arsenical alone (neoarsphenamine, mapharsen). (*b*) Of the two, mapharsen because of its low reactivity is the drug of choice, and 1200 mg. administered in 5 days, the optimum dose. (*c*) In seronegative primary syphilis, 90 to 100% pursue a satisfactory and uneventful course; without reference to type of drug or stage of disease, an aggregate of 81% secured a satisfactory result in one 5-day course, and one re-treatment in 15 cases raised the result to approximately

88% for the entire series (Leifer *et al.*). Elliott and co-workers estimated their curative results at at least 85% of all cases with early syphilis.

Adequacy of Treatment From the Standpoint of Service in the Armed Forces. A tentative basis for evaluation proposed for admission of registrants with syphilis to the United States Army is as follows:

Registrants with (1) confirmed positive serologic tests for syphilis and no clinical manifestations of the disease; or (2) with convincing histories of a trustworthy diagnosis of syphilis; or (3) of treatment for the disease on serologic or clinical grounds even though such evidence may possibly have been inadequate, may be considered for unlimited military service: (*a*) Provided that a negative spinal fluid since treatment was begun has been reported from a trustworthy source; and (*b*) provided that in infections estimated to be of less than 4 years duration, at least 30 to 40 arsenical and 40 to 60 insoluble bismuth injections or its equivalent with a minimum total of 75 injections have been given, with approximate continuity (no rest periods or lapses) during the first 30 weeks of treatment; and (*c*) provided that except as further qualified below in infections estimated to be over 4 years duration, at least 20 arsenical injections or its equivalent with a minimum total of 60 injections have been given in alternating courses; rest periods between consecutive courses not exceeding 8 weeks, being allowable.

Evidence of duration of the infection shall be weighed by the examiner with due regard for the age, general venereal history and medical guidance of the registrant.

In infections of *unknown duration* it shall be presumed for classification purposes that those of registrants under 26 years of age are of less than 4 years duration, and over 26 years of age, of more than 4 years duration.

In congenital infections and in acquired infections of more than 10 years known duration, in which no clinical progression occurred since treatment was begun; and in which a normal spinal fluid has been recorded at some time after treatment was begun and negative physical examination is recorded not less than 2 years after treatment was terminated, the infection shall be regarded as "quiescent," and the registrant eligible for unlimited military service; provided the treatment in question shall have included 20 arsenical and 20 heavy metal injections.

For the determination of treatment, the signed statements of acceptable treatment sources administering it with total number of doses of each drug and approximate calendar dates of administration and available laboratory and clinical data shall be required as evidence.

The Prognostic Significance of Secondary and Serologic Relapse. The following principles, based in the main upon the groups of material cited in connection with the criteria of adequacy of treatment for syphilis, are widely accepted. Early evidence of potentially unfavorable or relapsing course in an early syphilitic infection can be found in (*a*) failure of the primary or secondary lesions to heal under an arsenical therapy; (*b*) continued presence of *Sp. pallida* in the lesions after the employment of a known effective trivalent arsenical (these 2 groups constitute treatment resistance in syphilis;[30] (*c*) prematurely early reversal of a positive serologic reaction on the blood to negative (4th to 7th week in seropositive primary or secondary syphilis); (*d*) failure of a positive serologic reaction on the blood to reverse to negative after the 16th week (in the intensive or 5-day drip system reversal is ordinarily expected by quantitative tests between the 10th and 18th weeks after the institution of treatment but late secondaries may not reverse for many months even though "cured").

Cooperative Clinical Group results[12] (observation period too short) showed a relapse expectancy of 19.7% including all forms, of which, when observed for more than 6 months, 12.1% was mucocutaneous, 3.4% asymptomatic neurosyphilis, 4.1% symptomatic neurosyphilis, and 0.9% cardiovascular syphilis.

The unfavorable prognostic significance of early and intermediate relapse was well brought out in Padget's series in which "cure" was achieved in 73.2% of 456 patients in whom no relapse was observed, whereas only 28.2% of those sustaining an intermediate relapse achieved "cure". Persistent seropositive reactions on the blood, however, occurred in 16% of those who sustained no relapse, and in 10.3% of those who underwent intermediate relapse. Late benign syphilis developed 8 times as frequently in relapsers as in non-relapsers, cardiovascular syphilis

3.5 times as frequently; neurosyphilis 6 times as frequently; multiple late manifestations 7.5 times as frequently in relapsers as in non-relapsers. The occurrence of weak positive serologic reactions on the blood appearing in the course of a series of negatives in treated early syphilis have been emphasized as of relapse significance by certain authors.

Significance of Seropositivity After Treatment Which Was Begun During Early Syphilis. Broadly speaking, Padget's experience indicated that a residue of 14.9% persistent serologic positiveness would appear in a series of early syphilitics on whom the satisfactory results he described had been secured. In these cases there would be no manifestations such as abnormal spinal fluid, cardiovascular disease, visceral disease and so forth to accompany the persistent seropositiveness. The inclination would be, therefore, to rate it in these cases as without significance. In general, however, persistence of a positive serologic reaction on the blood of early syphilitics under treatment by the older standard continuous systems was an indication of presence of asymptomatic neurosyphilis, and called for an examination of the spinal fluid immediately.[25,48] The more intensive foreshortened treatment systems seem so materially to have reduced the likelihood of the occurrence of asymptomatic neurosyphilis that the neurosyphilitic significance of persistent seropositivity will probably be greatly reduced by their use. In addition, to asymptomatic neurosyphilis, syphilis of the cardiovascular system, often coming to recognition 5 or more years after the cessation of treatment, may be included in the prognostic significance of seropositiveness of a persistent type in early syphilis.

The Prevention of Cardiovascular Syphilis. This is still the *terra incognita* of modern syphilology and the studies thus far summarized have thrown relatively little light upon it. Langer[26] and others have attributed the increase in the incidence of aortitis since 1912 to the use of arsphenamine in the treatment of syphilis, but our experience with this drug in early syphilis fails to substantiate this belief, the incidence of recognizable aortic lesions not increasing materially in the period studied. It is, of course, true that our study does not extend forward into the period of maximum recognition of this form of syphilis. Moore, Danglade and Reisinger[29] in considering Langer's contention, believed that the apparent increase coincident with the use of arsphenamine in treatment is due rather to more accurate pathologic study with increasing knowledge of microscopic appearance of aortic syphilis. Progression of cardiovascular syphilis in spite of various methods of treatment occurred in 0.8% to 1.2% of our patients. Warthin's[49] observation, which placed the incidence of aortic syphilis in syphilitic adults between 1909 and 1919 at 97.6%, and between 1919 and 1929 at 86.3%, further supports the view that arsphenamine is not responsible for the apparently increasing incidence observed by Langer.

Moore and Padget[32] in their analysis of seroresistant syphilis (early) emphasize the seriousness of seroresistance in early syphilis and its relatively lesser significance in late syphilis. Twenty-three per cent of their seroresistant group sustained infectious relapse as against 5% who secured prompt serologic reversal. Neurosyphilis occurs in 31% of the seroresistant cases, but in only 18% of those who sustain prompt reversal.

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OTO-RHINO-LARYNGOLOGY

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THE LOCAL USE OF SULFONAMIDES IN NASAL AND SINUS INFECTION: AN ANALYTICAL REVIEW

By Noah D. Fabricant, M.D.

Earlier in the year Long[21] declared that the introduction of sulfonamide compounds as prophylactic and curative agents in the field of surgery has not been an unmitigated blessing for surgeons because of a growing tendency to neglect fundamental principles of good surgical judgment and technique and to rely instead on the wholesale use of the "wonder drugs." In a limited sense, this judgment is equally applicable to the promiscuous local use of sulfonamides in nasal and sinus infection; for here, many physicians neglect the sound physiologic principles upon which rational nasal and sinus medication rests.

Rhinologists, in recent years, have placed special stress on nasal physiology and nasal histopathology—subjects, incidentally, to which most nose and throat textbooks attach insufficient importance—because to a great extent these two fields provide the quintessence of intelligent intranasal medication. Since the magic word "sulfonamide" has stirred the collective hopes of a sinus-conscious public and a sinus-sensitive medical profession, the purpose of this review is to attempt an evaluation of the published results concerning the local use of sulfonamides in nasal and sinus infection so as to bridge the gap between what meager laboratory investigation there has been and eventual clinical judgment.

The wide acceptance of a rationalized form of nasal and sinus therapy by the medical profession can be established only in the event of a clear understanding of the manner in which drugs work. Such an understanding is assisted materially by studying the effect of drugs on several very important factors: the behavior of the mucous membrane lining of the nose, ciliary action, nasal pH, and the production of systemic side-effects. Nasal medication harmful to ciliary action impairs a highly important function. Markedly alkaline drugs are very irritating to the nasal mucous membrane; drugs prompting pathologic change in the underlying mucous membrane are agents to be avoided. Drugs which induce toxic reactions following intranasal medication are undesirable and merit small consideration in routine practice. Conversely, non-toxic medication, compatible with ciliary action, possessing a physiologic nasal pH and non-traumatizing to the mucous membrane, is most useful in the treatment of nasal and sinus disease—for it functions on a rational, physiologic basis.

Effect on Nasal Mucous Membrane and Nasal pH. According to Futch[13] and his associates, the complexity of chronic sinusitis is known too well to expect an eradication of infection, degenerative pathologic changes, and the constitutional factors involved by the use of a single medicament. Chronic sinusitis is not a specific disease, and success cannot be expected when it is so treated. Their report on the effect of solutions of sodium

sulfathiazole in 5% and 30% concentrations when applied to the nasal mucous membranes of rabbits is of interest. It was found that a 5% solution of sulfathiazole sesquihydrate exerts an early and destructive effect on the nasal mucous membrane. The cilia and the superficial layers of columnar cells are, to a large extent, destroyed. Even after 1 week's rest from instillations, recovery does not take place. Hydrogen-ion concentration determinations revealed that both the 5% and the 30% solutions had a pH of approximately 10.

The effect of sulfathiazole solutions instilled in the noses of inbred Swiss mice was recently described by Hunnicutt.[16] The mice were treated with 0.5%, 1% and 5% solutions of sodium sulfathiazole. Since the 5% solution had been recommended in the medical literature, more extensive experiments were carried on with it. Instillations were made 3 times a day for 14 days. In order to determine if there were any intermediary changes, 3 mice were killed every twenty-four hours, including the 10th day, and then a final group was killed on the 14th day. Purulent exudate was found during the first 3 days in about half of the mice; after that the only finding was a slight excess of mucus. The most pronounced change occurred in the olfactory epithelium which was disorganized even though it was not destroyed. The sinuses showed purulent exudate, and the epithelium, particularly that lining the frontal sinuses, was highly inflamed. In this early group, in which a purulent exudate and inflamed mucous membrane was present, a number of the mice developed bronchopneumonia. When applied to the nasal mucous membrane, 0.5% and 1% solutions of sodium sulfathiazole produced the same types of reactions although the inflammation was less.

Gundrum[14] utilized 21 rabbits—the rabbit was thought to present a mucous membrane more nearly compatible to that of human beings than the mucous membrane of any other laboratory animal—to observe and study the effect of 4.7% solutions of sodium sulfathiazole, sodium sulfadiazine and butanoylsulfanilamide on the nasal mucous membrane. There seemed to be considerable discomfort and restlessness after prolonged application of the sulfanilamide derivatives. At autopsy, in all of the animals treated with sulfanilamide derivatives there was evidence of inflammation throughout the nose. This was more marked in those animals in which sodium sulfathiazole and butanoylsulfanilamide were used. Microscopic study of the sections from the animals in the series treated with sodium sulfathiazole and the series treated with butanoylsulfanilamide showed injury to the entire nasal mucous membrane and the destruction appeared greatest in the olfactory area. Sodium sulfadiazine, while not so completely destructive, was found to be definitely injurious.

A hydrogen-ion concentration near that normal to the mucous membrane is, according to Fantus,[8] a matter of even greater importance for applications to the mucous membranes than the matter of isotonicity. In this connection, Fabricant[7a, b, c] has reported the normal, physiologic nasal pH values of the human being to be in the range between approximately pH 5.5 and 6.5. He has suggested that during an attack of acute rhinitis, acute rhinosinusitis and the more active stages of allergic rhinitis, the employment of an appropriate nasal medicament which lowers the abnormal, alkaline pH found in these conditions to a normal, slightly acid level between 5.5 and 6.5—in short, a physiologic pH—is most desirable. Since the sodium salts of the sulfanilamide group are extremely alkaline, having a pH which ranges from 10 to 11, they are by no means free of undesirable caustic reactions because of the irritating properties associated

with its alkalinity. In addition to these unfavorable features, a further objection to their use has been the fact that solutions of sulfathiazole may become yellow on standing and decompose within a few days, especially when unprotected from daylight.

At the time Turnbull[32] overenthusiastically advocated the use by nasal spray of a 5% solution of sodium sulfathiazole in the treatment of chronic sinusitis, many physicians began a mass clinical trial before adequate laboratory investigation of the type just described had been undertaken. A warning, however, came from Fletcher,[10] who reported necrosis of the lining of the maxillary sinus following irrigations of the sinus with 5% and 10% solutions of sodium sulfathiazole over a 3 week period. He maintained that inasmuch as the sodium salts of sulfanilamide derivatives are extremely alkaline, they are very caustic, and in this case the solutions charred or burned the granulations and mucous membrane with which they came in contact.

The use of a 5% solution of sodium sulfathiazole by means of nasal tamponage Merica[24] found to be quite disappointing in cases of acute rhinitis but effective in certain types of sinusitis. Following the application of 5% cocaine solution, Merica employed nasal tampons moistened with sulfathiazole solution. In this connection, it is of interest to note that the preliminary use of cocaine solution produced anesthesia of the nasal mucous membrane as well as an acid nasal pH environment.[7b] These two factors alone would be sufficient to counteract the usual intranasal distress produced by sodium sulfathiazole solutions. Despite the combined use of cocaine solution and sodium sulfathiazole solution, Merica observed some patients who did not tolerate the application; these patients developed reactions resembling an allergic rhinitis. A similar phenomenon has been noted by Bordley[2] and his associates. According to Fenton,[9] none of the combinations of sulfathiazole with vasoconstrictors is free from the possibility that allergic responses may be excited in susceptible persons, and it does not seem possible to determine in advance whether such sensitivity exists.

To obviate the strong alkalinity, irritating properties and deterioration of such solutions as have been discussed, Yonkman[35] and his associates have dissolved various sulfonamides in propylene glycol. The most useful of these propylene glycol preparations they believe to be a combination with a 3% solution of sulfathiazole, 3% solution of sulfapyridine and a 10% solution of sulfanilamide. The pH of these solutions is slightly acid and approximates normal, physiologic nasal pH values. Blackford[1] found a 3% solution of sulfathiazole in propylene glycol when used locally to be non-irritating and non-toxic. The preparation can be used generally in large amounts without untoward results. However, he believes further experimentation should be done in regard to the effect of this preparation on the ciliary action in the nose before any definite conclusions as to the advisability of using it extensively in acute upper respiratory infections can be drawn. Stovin[30] finds that a combination of sulfanilamide and allantoin lends itself to use in intranasal therapy; it is slightly acid with a pH of 5.4. Colloidal silver preparations of sulfanilamide, sulfathiazole, sulfapyridine and sulfadiazine have been investigated by Wruble.[34] With the exception of the silver sulfanilamide, which darkens rapidly, the others remain as white or cream-white powders, easily dispersible in water. Solutions of colloidal silver sulfathiazole have a slightly acid pH which is in the range of maximum effectiveness. It is possible that such non-irritant chemical combinations of the sulfonamides, after further study, may in time prove useful.

Clinical Reports. A small but steady stream of clinical reports[3, 19, 22, 28] has appeared in the medical literature. In attempting to establish the usefulness of local applications of sulfonamides to infections of the nose and sinuses, the preponderant majority of writers appear to neglect the entire body of knowledge known as nasal physiology. That the local administration of chemotherapeutic agents is substantially without influence upon the common cold is almost generally agreed. Since the literature on their value in sinusitis is still limited, the cross-currents of opinion preclude final judgment. At this juncture, it is well to remember that over a span of many years numerous agents have been introduced into the sinuses—particularly the maxillary sinus—immediately after lavage. The very multiplicity of these agents indicates the inadequacy of many of them; this is in itself evidence that the ideal treatment has not been found.

It was Turnbull[32] who first described the intranasal use of a 5% solution of sodium sulfathiazole in chronic sinusitis. After instilling it directly into the sphenoid and maxillary sinuses, he was unable to draw any conclusions regarding clinical improvement; but after spraying the nose, he saw definite improvement clinically. It is possible that what was observed as increased drainage from the nose following sulfathiazole spraying was in all likelihood due to the irritating qualities of the markedly alkaline medication rather than a free flow of discharge from the sinuses.

Bordley[2] and his associates believe that many nose and sinus complications may be prevented by spraying the nasal passages and pharynx with a 2.5% sulfadiazine triethanolamine solution. The concentration of sulfadiazine in the mucous membranes of the upper passages was not determined. Brown[4] finds that sulfonamide powder may be applied to the mucous membrane of the sinuses by the intranasal route and that the powder seems to be more effective than the solution in cases of chronic purulent sinusitis, probably because of its more lasting contact with the mucous membrane. Connell and Trowbridge[6] maintain that acute nasal infections respond best to the local use of sulfanilamide powder and chronic rhinitis best to sulfathiazole powder. It was found that coarse powder was not adaptable for use in the nasal cavities. Moderately fine or fine powder, of a 40 to 100 mesh character, proved to be the most satisfactory. Marks[23] states that a 20% or 50% sulfathiazole jelly is an effective therapeutic agent when injected into the maxillary sinus in which there is evidence of chronic maxillary sinusitis. A suspension of sulfathiazole appeared more effective than sodium sulfathiazole in clinical practice. Van Alyea,[33] however, questions the value of sulfonamide preparations instilled locally into the maxillary sinus. Kern[18] is of the opinion that sulfanilamide and gauze packing can be used satisfactorily after submucous resection, ethmoidectomy, and intranasal antrotomy. When the packing is removed in 24 hours, there seems to be less swelling of the mucous membrane and more rapid healing. Freeman[11] describes a method of treating acute infections of the nasopharynx and pharynx. He writes that the possibility of systemic damage from the use of sulfathiazole is negligible and can be carried out on ambulatory patients.

Lindsay[20] asserts that in chronic suppuration of the maxillary, frontal and ethmoid sinuses, he was unable to satisfy himself that sulfathiazole used locally after irrigation was of any definite benefit. He employed suspensions of finely ground sulfathiazole, in concentrations up to 30%, which could be introduced through a cannula. In treatment of acute infections of the sinuses, Lindsay declares, the suppuration is seldom limited to one sinus; there is usually more or less general infection of the upper respiratory

tract, with involvement of several sinuses. Therefore the treatment, for example, of the maxillary sinus alone cannot be expected to relieve the accompanying inflammatory process in the anterior ethmoid cells, or in the upper respiratory tract in general. The use of a 2.5% solution of sulfadiazine (with triethanolamine) as a spray did not shorten the course of sinus infection. The material was employed in a few cases by the displacement method and produced fairly severe discomfort, lasting nearly 24 hours. The pH of the solution is about 8.5, and attempts to lower the percentage of triethanolamine so as to reduce the pH have caused precipitation. It is believed that the local use of sulfonamide compounds does have a place in postoperative treatment of sinuses where a radical operation has been performed with removal of diseased mucous membrane. The effects here are similar to those in surgical wounds elsewhere, and the action in keeping down infection is unmistakable. In Furstenberg's[12] experience, sulfanilamide when used locally in septic wounds tends to shorten the period of convalescence, prevent troublesome local reactions and allay discomfort. It is unnecessary and undesirable to use it in a clean wound. Confidence in local chemotherapy is justified only when it is employed as an adjunct to an operation which is performed with credit to the surgeon and safety to the patient.

A recent publication of Silcox and Schenck[29] concerns itself with the use of microcrystalline forms of drugs of the sulfanilamide group. Their clinical study included patients treated with the microcrystals of a drug of the sulfanilamide group in 5% suspension in a physiologic solution of sodium chloride and a group of patients treated with microcrystals of sulfathiazole in a 5% suspension in 1% aqueous solution of paredrine hydrobromide (p-hydroxy-a-methylphenethylamine hydrobromide) which has a vasoconstrictor action. Levels of sulfathiazole in the blood taken in some of the early cases convinced the investigators of the comparative safety with which drugs of the sulfanilamide group can be used locally. No studies were made to determine the effect of the drug histologically on the nasal mucous membrane. In the group treated with a suspension of sulfathiazole in a solution of paredrine hydrobromide there was a rise in systolic blood pressure of 10 to 15 points after displacement irrigation. Microcrystalline preparations were found to be effective in the treatment of acute infections of the upper respiratory tract, of acute sinusitis, and in selected cases of chronic sinusitis. Sulman[31] used a suspension of sulfathiazole in an aqueous solution of paredrine hydrobromide and found it to be successful in reducing nasal congestion and in decreasing or eliminating discharge. No untoward effects of any kind were observed. Its use was believed to have shortened the course of infection for many patients and averted sequelæ to colds. Toxic reactions produced by this preparation are described as occurring in 2 cases by O'Donnell.[25]

Harris[15] and his associates discuss their experiences with the administration of sulfonamides by inhalation, by introducing sulfonamide "smoke" into the air. The "smoke" utilized in these experiments was derived from a 5% aqueous suspension of sulfathiazole microcrystals. The suspension was introduced into an atomizer supplied with compressed air which produced a finely divided spray. The resultant spray was led into a chamber containing Swiss white mice. Gross examination of the lungs at different intervals up to several days after the inhalation revealed mild hyperemia soon after the inhalation. Mice exposed to a spray of sodium sulfathiazole solution under similar conditions died within a few hours

and their lungs showed gross evidences of an extreme hyperemia. According to the authors, the pharmacologic experiments demonstrate that sulfathiazole can be administered by inhalation and produce satisfactory blood levels. Elsewhere,[5] it is stated by one of the investigators that three deep breaths in the adult taken while the "smoke" is being blown through the nose and/or mouth produce a sulfonamide blood level of 3 to 5 mg. per 100 cc. of blood in less than 15 minutes, as measured at the finger-tip. This level rises for some hours to approximately double the original figures and at the end of 2 days is usually still above 1 mg. per 100 cc.

Ivy and Goetzl[17] review the literature on the pharmacology of the drug known as d-desoxyephedrine hydrochloride. Recently the vasoconstrictor dl-desoxyephedrine hydrochloride, 0.125%, has been combined with 2.5% solution sodium sulfathiazole and is available for use in the nose and paranasal sinuses. A review of the literature indicates that d-desoxyephedrine hydrochloride has an action on man and on animals similar to that of amphetamine sulfate. It is more potent per milligram than amphetamine sulfate. Although a number of German authors have stated that d-desoxyephedrine hydrochloride is not habit-forming, it was placed under the German narcotic law with the warning that the physician employing it should exercise caution.

Among the case records of the Massachusetts General Hospital[27] is one dealing with an allergic middle-aged woman who had applied over a period of weeks sulfathiazole ointment to a fissure at the tip of the nasal ala. Prior to hospitalization she had also taken sulfathiazole by mouth. When a generalized skin eruption developed, she was admitted to a community hospital. She failed to respond to appropriate therapy and died of a "sulfathiazole nephritis." At the subsequent clinicopathologic conference the question of the treatment of the fissure about the tip of the ala with sulfathiazole ointment in a patient known to be allergic was raised. "Unless one believed that was a potentially dangerous lesion, which it could be if badly infected, one should not run the risk of sensitizing a person to a drug that may be a life-saving one later."

Comment. The haste with which some members of the medical profession and the general public have responded to the cry that the local use of sulfonamides in nasal and sinus infection is an effective "cure-all" is not without some apparent danger. Knowledge of the normal physiology of the lining mucous membrane of the nose and sinuses received its chief impetus in this country from the studies of a number of American investigators. Despite their efforts to familiarize physicians with the importance of nasal physiology and its immediate relationship to rational, physiologic nasal medication, certain fundamental principles appear to have been overlooked in the local application of various sulfonamide preparations indiscriminately employed in nasal and sinus infection.

Such factors as the effect of a nasal medicament on the mucous membranes of the nose and sinuses, its relationship to ciliary action and nasal pH, and the degree of toxicity which is sometimes produced by absorption from the mucous membrane are always of propitious consideration in establishing the value of a nasal preparation. The fact that alkaline preparations of sodium sulfathiazole solutions injure the mucous membrane is sufficient to indict it on that score. Furthermore, the destruction of cilia—and consequently the impairment of ciliary function—together with its deviation from a physiologic nasal pH, as well as the disorganization of the olfactory epithelium which such preparations establish, plus

the production of bronchopneumonia in laboratory animals, cannot justify the indiscriminate selection of sodium sulfathiazole preparations for use in the human nose.

The recent introduction of a number of sulfathiazole preparations in alkaline combination with a nasal vasoconstrictor raises several pertinent questions. Nasal vasoconstrictors, Proetz[36] declares, are probably the most important single group of drugs available to the rhinologist. In terms of clinical evaluation, it is therefore extremely difficult to interpret the benefits to be gained by a patient receiving a form of combined intranasal medication. The vasoconstrictor action of some nasal vasoconstrictors is powerful and may conceivably lead to a partial, and in some cases, total (although transitory) anoxia. Some of the cells may suffer damage, but this is reparable with the decrease of the vasoconstrictor effect. It is possible that the damage might be more if the sulfonamide preparations are present. In any event, there is need for further evidence of its innocuousness other than a simple clinical observation.

The degree of toxicity that may be produced by sulfonamides is equally deserving of scrutiny. Patients employing sulfonamides locally are potentially subject to all the risks entailed by oral or parenteral administration. In a therapeutic field as new as this, physicians should be on their guard as to the possibility of such complications as allergic rhinitis, toxic dermatitis, jaundice, hematuria, blood dyscrasias, hyperpyrexia, central nervous system effects, weakness and pallor, and nausea and vomiting. Finally, unintelligent and promiscuous usage locally of sulfonamide preparations may develop in the patient a sulfa-resistant state. In general, such resistance is by no means a theoretical matter.

With respect to the rôle of the local use of sulfonamides in nasal and sinus infection, the clinician should not on the basis of inconclusive clinical evidence run too far ahead of competent and painstaking laboratory evidence. While the evidence to date would seem to indicate caution in the use of some of the sulfonamide preparations in the nose and sinuses, others are employed successfully in a limited number of directions. These do have an important place in contemporary rhinology. Indeed, it is quite possible that the near future may see the further introduction of sulfonamide preparations which locally are non-toxic and which are compatible with the tenor of modern-day nasal physiology. Such agents, however, may in time prove useful only as an important adjunct to the effective treatment of nasal and sinus infection, rather than as a universal "cure-all."

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BOOK REVIEWS AND NOTICES

THE MEDICAL CLINICS OF NORTH AMERICA. Symposium on Infectious and Tropical Diseases. (Vol. 27, No. 3, May 1943.) Pp. 881; many illus. Philadelphia: W. B. Saunders Company, 1943. Price, year, $16.00.

THIS number is especially welcome at this time, offering as it does concise and authoritative reviews on a number of the most important tropical diseases, as well as on certain other borderline diseases. The discussions aim at being practical rather than exhaustive, yet space has been found to present the newest and most up-to-date conceptions of transmission, diagnosis and treatment. Preventive aspects are also stressed, as would be expected from a group of contributors, many of whom are workers in the field of Public Health or Preventive Medicine.

The subjects on the whole are well chosen, prominence being given to malaria and dysentery, typhus and relapsing fever, all diseases which may easily assume epidemic proportions with our armed forces. The Reviewer would have been pleased to see a fuller discussion of the dysenteries, but doubtless space forbade. Trypanosomiasis, filariasis, schistosomiasis, dengue, plague and cholera are discussed by masters in the field, the presentations coming to us out of years of personal experience in many instances. The names of Dyer, Strong, Simmons and Russell, to mention but a few, are evidence of the authoritative character of the contributions. It would be impossible to cover the whole field of tropical diseases in one slender volume, and further volumes to supplement these studies would be very desirable.

It seems not inappropriate at this time when tropical diseases are being brought to America in increasing numbers, to find them discussed side by side with other infectious diseases which cause much concern in the United States. Among these latter are the epidemic encephalitides, coccidiodomycosis and primary atypical pneumonia. Well-known workers in these fields crystallize for us the recent knowledge and views on each subject. Late reports and conclusions regarding diseases longer known to the medical profession form the basis for other valuable articles and round out a series of unusual significance. No doctor would wish to miss an acquaintance with this symposium on infectious and tropical diseases. J. M.

THE NEUROMUSCULAR MATURATION OF THE HUMAN INFANT. By MYRTLE B. MCGRAW, Associate Director, the Normal Child Development Study, Department of Pediatrics, Columbia-Presbyterian Medical Center. Pp. 154; some illustrations. Morningside Heights, N. Y.: Columbia University Press, 1943. Price, $2.00.

THE studies reported in this volume cover more than a decade of observation on the development of function in the newborn and infant child. The investigation originated in an attempt to correlate the development of activity with the anatomic maturation of the cells of the human cortex, a problem upon which Dr. Frederick Tilney was working before his death.

The general plan was to examine some particular function, for example, the behavior of the child in water, and trace the development of this behavior until a point was reached in which deliberate or voluntary control appeared to be exercised on that function. At this time, it was assumed by Dr. McGraw, the cerebral cortex began exerting its effect. For example, the newborn child, when placed in water, will swim, reflexly it is presumed. At a later date this type of activity gives way to disorganized, struggling movements; and still later, to voluntary swimming.

The various actions studied cover the range of early motor behavior in the

infant. Among these are: grasping, postural reflexes, rolling over, crawling, creeping, sitting, rising, and walking.

Due to Dr. Tilney's untimely death, the anatomic evidence on the maturation of the human cortex is still lacking, so that the author's original aim has not been achieved. Nevertheless some conclusions have emerged from this study which will appeal to a wider audience than her original thesis would interest.

Dr. McGraw suggests that her studies point the way to a better method of training children. Among her conclusions are: it is futile to attempt training before the neural mechanisms have developed sufficiently; exercise of a newly developing function may advance the achievement beyond the stage normally expected; transition from one type of activity to another is characterized by disorganization and confusion; the behavior pattern will tell when a child is ready to undertake a new type of activity; it is just as important to know when to diminish training as when to begin it. Obviously the conclusions from a study of these motor actions are in some way applicable to more complicated intellectual development.

This work can be commended highly for its succinct summary of these important studies. G. G.

LABORATORY EXPERIMENTS IN PHYSIOLOGY. By W. D. ZOETHOUT, PH.D., Professor of Physiology in the Chicago College of Dental Surgery (Loyola University). Third ed. Pp. 256; 88 illus. St. Louis: The C. V. Mosby Company, 1943. Price, $2.25.

A DESCRIPTION of apparatus commonly used in the elementary physiology laboratory is followed by procedures for an ample number of simple experiments illustrating fundamental physiological principles, stressing the nerve muscle, cardiovascular, respiratory systems, and special senses. Judicious selection of experiments from this manual should result in an adequate laboratory accompaniment to a course in elementary physiology for college or dental school. For the most part, apparatus illustrated and described is made by the Harvard Apparatus Company, but the experiments are adaptable to other types.

Part II of the manual consists of a few simple experiments of a chemical nature illustrating tests for carbohydrates, fats, and proteins, the fundamentals of digestion, and of urinalysis. A. C.

BLOOD GROUPS AND TRANSFUSION. By ALEXANDER S. WIENER, A.B., M.D., Serologist and Bacteriologist in the Office of the Chief Medical Examiner of New York City, Head of Transfusion Division, Jewish Hospital of Brooklyn, New York. Third ed. Pp. 438; 69 figs., 106 tables. Springfield, Ill., and Baltimore, Md.: Charles C Thomas, 1943. Price, $7.50.

IN every hospital's experience transfusion reactions of the hemolytic type occur more frequently than textbook statistics would indicate, even when the technique of administration lies above reproach. Fortunately the symptoms are usually but slight or moderate, though violent and even fatal "accidents" are noted at times. Any such reaction is not only potentially dangerous; its presence signifies that the administered blood has been destroyed, wholly or in part, and to that extent the therapeutic intention of the transfusion has not been achieved. The only way to assure complete safety and efficiency with every transfusion is to give the physicians in charge a full understanding of the complementary sciences of transfusion and of grouping.

For this reason one welcomes the publication of the third and thoroughly up-to-date edition of this well-known authoritative monograph, with its excellently organized body of information and interpretation. The first third of the book discusses in detail the properties of the known blood agglutinogens, not only A and B but also A_2, A_3, M, N, P, Rh and Hr, singly and in combination. Included are chapters on sources of error in blood grouping, history

and techniques of blood transfusion, reactions and complications following transfusion, and the preparation and storage of blood, plasma and serum. Next comes a learned but extremely readable presentation of the individual differences in human (and animal) bloods in relation to heredity and anthropology. Statistics have been kept to a minimum, with the symbols and methods used explained lucidly in advance. The final portion of the book deals with recent progress, such as the important relationship of the Rh factor to erythroblastosis fetalis and to hemolytic reactions during pregnancy or after multiple transfusions. Medico-legal applications of blood tests in disputed parentage, and the individual identification of stains in forensic cases, are gone into extensively. All chapters reflect the wealth of experience of the author.

I. W.

THE PRACTICE OF REFRACTION. By SIR STEWART DUKE-ELDER, M.A., D.Sc. (ST. AND.), PH.D. (LOND.), M.D., CH.B., F.R.C.S., Surgeon-Oculist to H. M. The King; Ophthalmic Surgeon and Lecturer in Ophthalmology, St. George's Hospital. Fourth ed. Pp. 328; 183 illus. Philadelphia: The Blakiston Company, 1943. Price, $4.50.

THE aim of this book, as of the 3d edition from which it differs in only minor respects, is to present the essential principles of the theory and practice of the correction of defects in the optical system of the eyes and their associated muscles. Clinical methods and criteria are stressed. Not undue emphasis is laid upon the consideration of the general bodily welfare as well as the local ocular state. The subject of aniseikonia is introduced. Many in this country would disagree with the author concerning the use of orthoptics and/or surgery in cases of squint. And, also, many would use cycloplegics more freely than he recommends. On the whole, however, the book is a valuable addition to the library of one familiar with the subject, as well as that of the beginner.

P. M.

TABLES OF FOOD VALUES. By ALICE V. BRADLEY, M.S., Associate Professor of Nutrition and Health Education, State College, Santa Barbara, Calif. Pp. 224. Second ed. Peoria, Ill.: The Manual Arts Press, 1942. Price, $3.50.

THIS is an excellent book for the purpose for which it is intended, namely "to calculate an individual's diet quickly in an approximate way."

The book is easily read; the figures are large enough to be quickly read and the naming of foods on each side of the tables is a big aid for speed. The tables are comprehensive and the many recipes included certainly add to the value of the book for the lay person. The fact that the tables give both the weight in grams and the approximate measure adds to the value of the book for everyone using it.

E. M.

CLINICAL ROENTGENOLOGY OF THE CARDIOVASCULAR SYSTEM. By HUGO ROESLER, M.D., F.A.C.P., Temple University School of Medicine, Temple University Hospital, Philadelphia. Second ed. Pp. 480; 337 figs. Springfield, Ill.: Charles C Thomas, 1943. Price, $7.50.

THIS 2d edition brings up to date the most comprehensive presentation of the subject in the English language. The technique and apparatus used in the various methods of roentgenologic study; the anatomy, physiology and roentgenologic aspects of the normal and abnormal cardiovascular apparatus and its subdivisions; cardiovascular disease from the viewpoint of etiology and structural changes and methods of measurement are all adequately discussed and well illustrated. Their integration with clinical data makes the book particularly valuable. A full bibliography with each chapter and a good index are appended. The following suggestions are offered for improvement of a future edition: the use of the terms "dorsad" and "ventrad" is somewhat

confusing and stilted in view of man's erect posture and the widely accepted use of the terms "anterior" and "posterior"; the use of numerous black and white arrows instead of numbers in many of the illustrations requires a tedious search in the lengthy captions for identification; despite the author's fear of breaking continuity, specific facts in the text should be numerically related to the chapter bibliographies to enhance the value of the book as a ready reference text. However, the book is unreservedly recommended as required reading for students of roentgenology and cardiovascular disease. A. M.

FLYING MEN AND MEDICINE. The Effects of Flying Upon the Human Body. By E. OSMUN BARR, M.D. Pp. 254; 8 figs, 1 colored plate. New York and London: Funk & Wagnalls Company, 1943. Price, $2.50.

AN interesting and adroitly written book about aviation medicine in unusually simple language for the non-technical reader. Anyone who wishes to catch up on this most recent aspect of medicine without being overburdened by a mass of physiologic and technical details should read this entertaining volume. It is sufficiently complete and contains many interesting and instructive diagrams. The book is especially recommended to the young aspirant for wings. W. S.

RENAL LITHIASIS. By CHARLES C. HIGGINS, M.D., Cleveland Clinic, Cleveland, O. Pp. 122; 18 illus. Springfield, Ill.: Charles C Thomas, 1943. Price, $3.00.

THIS brief treatise, the annual Beaumont Lecture for 1942, is by a recognized authority on renal lithiasis. The author, an assiduous research worker, has given us something which is a pleasure to read. Dr. Higgins writes with the authority of years of clinical experience, and backed by the entire research personnel of the Cleveland Clinic.

Starting with a delightful though brief history of renal lithiasis, he follows with a lucid exposition of the etiology, always leaning toward his own belief in the part played by diet and vitamin A deficiency. There follow 7 pages on symptomatology, 15 devoted to the surgical handling of the problem, and 15 more on the dietary treatment. The book ends with 16 pages devoted to recommended diets for restricting the intake of unwanted salts, for increasing the vitamin A, and for acidifying or alkalinizing the urine. A. R.

UROLOGY IN GENERAL PRACTICE. By NELSE F. OCKERBLAD, B.S., M.D., F.A.C.S., Professor of Clinical Urology, University of Kansas School of Medicine; Senior Attending Urologist to St. Luke's Hospital; Consulting Urologist to the Children's Mercy Hospital, Kansas City, Mo.; and HJALMAR E. CARLSON, B.S., A.M., M.D., F.A.C.S., Instructor in Urology, University of Kansas School of Medicine; Attending Urologist to St. Luke's Hospital and Trinity Hospital, Kansas City, Mo. Pp. 383; 98 figs. Chicago: Year Book Pub., 1943. Price, $4.00.

THIS small, practical manual should be useful as an easily read outline of the subject to student, practitioner, and specialist.

There is a chapter on urologic diagnosis which gives one a well-balanced idea of the approach to the urologic patient. The information presented should help a physician to decide which cases can be best taken care of by the general practitioner and which cases require the care of experts in the field.

The use and care of catheters, sounds, and other diagnostic and therapeutic urologic equipment are discussed. Contraindications to the use of such materials are presented.

The discussion of the various diseases of the urinary organs is thorough and important practical points in the diagnosis and treatment are given. There is

a separate chapter on the so-called "medical diseases" of the kidney. The authors think that nephritis and allied conditions are best handled under the supervision of the urologist.

The discussion of urinary lithiasis contains the usual information presented on the subject and in addition mentions the most recent contribution to the knowledge of the etiology of urinary stone, that is Randall's papillary lesion.

There is an entire chapter devoted to carcinoma of the prostate. This one-time therapeutic enigma can be so handled that these patients can live on with a fairly normal existence. Treatment with stilbestrol and bilateral orchidectomy is discussed.

The chapters on the use of sulfonamides in urologic infections, both gonorrheal and non-specific, are a bit sketchy considering the great advance that the introduction of these substances afforded. The proprietary drug "sulamyd" is recommended by the authors on several occasions for the treatment of non-specific types of urinary infections; but evidence in the literature and from those who have had personal experience in the use of this drug would not indicate that its therapeutic effects warrant such high esteem as here presented.

The inclusion of a bibliography would increase the value of the book to anyone desiring further information on any subject presented. L. LA T.

AN INTRODUCTION TO GROUP THERAPY. By S. R. SLAVSON, Director of Group Therapy, Jewish Board of Guardians, New York, formerly Lecturer, School of Education, New York University. Pp. 352. New York: The Commonwealth Fund, 1943. Price, $2.00.

THIS book is the outgrowth of 8 years' experience of the Jewish Board of Guardians of New York City. Group therapy is "not merely group activity but a method of psychotherapy to be employed along with psychiatric case work and psychologic services and only after a diagnostic examination indicates that it is needed." It may be used as exclusive treatment or as supplementary to individual treatment.

The principles and practices of group therapy are described and descriptions of actual cases and case treatments are given. This book should be of great value not only to the clinical worker but to teachers and administrators in our schools. It reveals unsuspected values in group work that may be very suggestive in the pupil activity program even though many of the specific methods described would be quite unsafe in the hands of a teacher untrained in psychiatric case work. A. J.

A MANUAL OF PULMONARY TUBERCULOSIS (PART I) AND AN ATLAS OF THORACIC ROENTGENOLOGY (PART II). By DAVID O. N. LINDBERG, M.D., F.A.C.P., Lecturer on Tuberculosis, State University of Iowa, College of Medicine. Pp. 219; 189 illus. Springfield, Ill.: Charles C Thomas, 1943. Price, $6.50.

IN this book Part I presents a discussion of the diagnosis and treatment of pulmonary tuberculosis and the author has wisely included a chapter dealing with modern methods of control. Numerous charts and graphs are used to good advantage and the illustrations are of excellent quality. Part II is purely an atlas of radiographic reproductions comprising 145 plates. The roentgenologic aspects of tuberculous pulmonary disease are amply portrayed, including results following treatment by conservative measures as well as by various surgical procedures. In addition, the characteristic radiologic findings of many of the more frequently encountered intrathoracic lesions other than tuberculosis are also presented. The plates are uniformly good.

Although the author emphasizes his desire for "brevity and sequence" and avoidance of "theoretical, experimental or controversial subjects," it would seem that the extreme brevity, so obvious in certain portions of the text, has detracted from the value of this work. However, the material is presented in a concise manner and clarity has been maintained throughout. H. I.

NEW BOOKS

An Atlas of Anatomy. By J. C. Boileau Grant, M.C., M.B., Ch.B., F.R.C.S. (Edin.), Professor of Anatomy in the University of Toronto. Vol. 1, Upper Limb, Abdomen, Perineum, Pelvis, and Lower Limb. Pp. 214; 227 figs. Baltimore: The Williams & Wilkins Company, 1943. Price, $5.00.

The Conquest of Epidemic Disease. A Chapter in the History of Ideas. By Charles-Edward Amory Winslow. Pp. 411. Princeton, N. J.: Princeton University Press, 1943. Price, $4.50.

Hospital Discharge Study. Vol. 2, Hospitalized Illness in New York City. By Neva R. Deardorff, Ph.D., and Marta Fraenkel, M.D. Pp. 349; 105 tables. Welfare Council of New York City, 1943. Price, $1.00.

This report is the second of the 3 volume publication *Hospital Discharge Study* (an analysis of 546,623 patients discharged from hospitals in New York City in 1933). It abstracts and studies 24 items of information on these patients covering their medical, demographic and social conditions and certain details on hospital stay. The volume contains a wealth of statistical information and demonstrates the value of and need for a more intensive study of hospital records. R. B.

Papers From the Second American Congress on General Semantics. Non-Aristotelian Methodology (Applied) for Sanity in our Time. Compiled and Edited by M. Kendig. Pp. 579. Chicago: Institute of General Semantics, 1943. Price, $5.00.

Reconstructive Surgery of the Eyelids. By Wendell L. Hughes, M.D., F.A.C.S., Hempstead, N. Y. Pp. 160; 36 plates. St. Louis: C. V. Mosby Company, 1943. Price, $4.00.

Self-teaching Tests in Arithmetic for Nurses. By Ruth W. Jessee, R.N., M.A. Pp. 111. St. Louis: C. V. Mosby Company, 1943. Price, $1.50.

Kaiser Wakes the Doctors. By Paul de Kruif. Pp. 158. New York: Harcourt, Brace & Co., 1943. Price, $2.00.

Doctor Pryor: An Autobiography. By Dr. J. W. Pryor. Pp. 312; 17 illus. Cynthiana, Ky.: The Hobson Press, 1943. Price, $3.00.

Applied Anatomy of the Head and Neck. For Students and Practitioners of Dentistry. By Harry H. Shapiro, D.M.D., Assistant Professor of Anatomy, College of Physicians and Surgeons, Columbia University. Pp. 189; 173 illus. Philadelphia, London, Montreal: J. B. Lippincott Company, 1943. Price, $5.50.

Essays in Biology. In Honor of Herbert M. Evans. Written by His Friends. Pp. 687; many illus. Berkeley and Los Angeles: University of California Press, 1943. Price, $10.00.

NEW EDITIONS

Chemical Spectroscopy. By Wallace R. Brode, Professor of Chemistry in the Ohio State University. Second ed. Pp. 677; 41 plates. New York: John Wiley & Sons, Inc., 1943. Price, $7.50.

An Introduction to Sociology and Social Problems. By Deborah M. Jensen, R.N., B.Sc., M.A., Instructor in Sociology and Social Problems at Schools of Nursing of St. Louis City Hospital and St. Luke's Hospital; Lecturer in Nursing Education, Washington University; Formerly Social Service Consultant to the Visiting Nurse Association, St. Louis. Second ed. Pp. 420; 78 figs. St. Louis: C. V. Mosby Company, 1943. Price, $3.25.

Family Nutrition. Published by the Philadelphia Child Health Society, 311 S. Juniper St., Philadelphia 7, Pa. Pp. 119; many tables and figures. Second ed. Price, 50 cents (special prices on quantity orders of 10 copies and more).

In 1942 the 1st edition of the monograph was published by the Philadelphia Child Health Society. Since that time, additional needs have become important enough to publish a 2d edition of this booklet a year later. Much of the material is essentially the same as in the 1st edition—the important addition being a chapter on menu planning and rationing for wartime nutrition needs. The other chapters and tables have been brought up to date. E. F.

Notice to Contributors. Manuscripts intended for publication in the AMERICAN JOURNAL OF THE MEDICAL SCIENCES, and correspondence, should be sent to the Editor, DR. EDWARD B. KRUMBHAAR, School of Medicine, University of Pennsylvania, Philadelphia 4, Pa. Articles are accepted for publication in the AMERICAN JOURNAL OF THE MEDICAL SCIENCES exclusively, except in the case of subsequent publication in Society proceedings.

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For the balance of the war, 150 reprints will be supplied gratis. Covers will be omitted on all articles. In ordering additional reprints, we will supply in multiples of 150. This modification is for the same reason as the change of format, *i. e.*, conservation of paper.